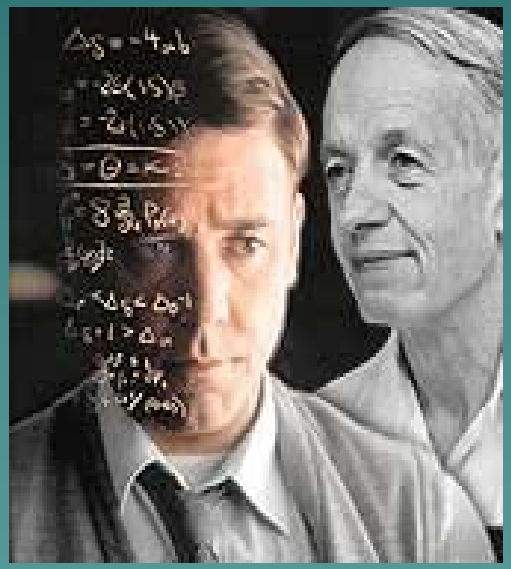
Transdisciplinary Imaging Genetics Center

Steven G. Potkin

UC Irvine

Schizophrenia as a model



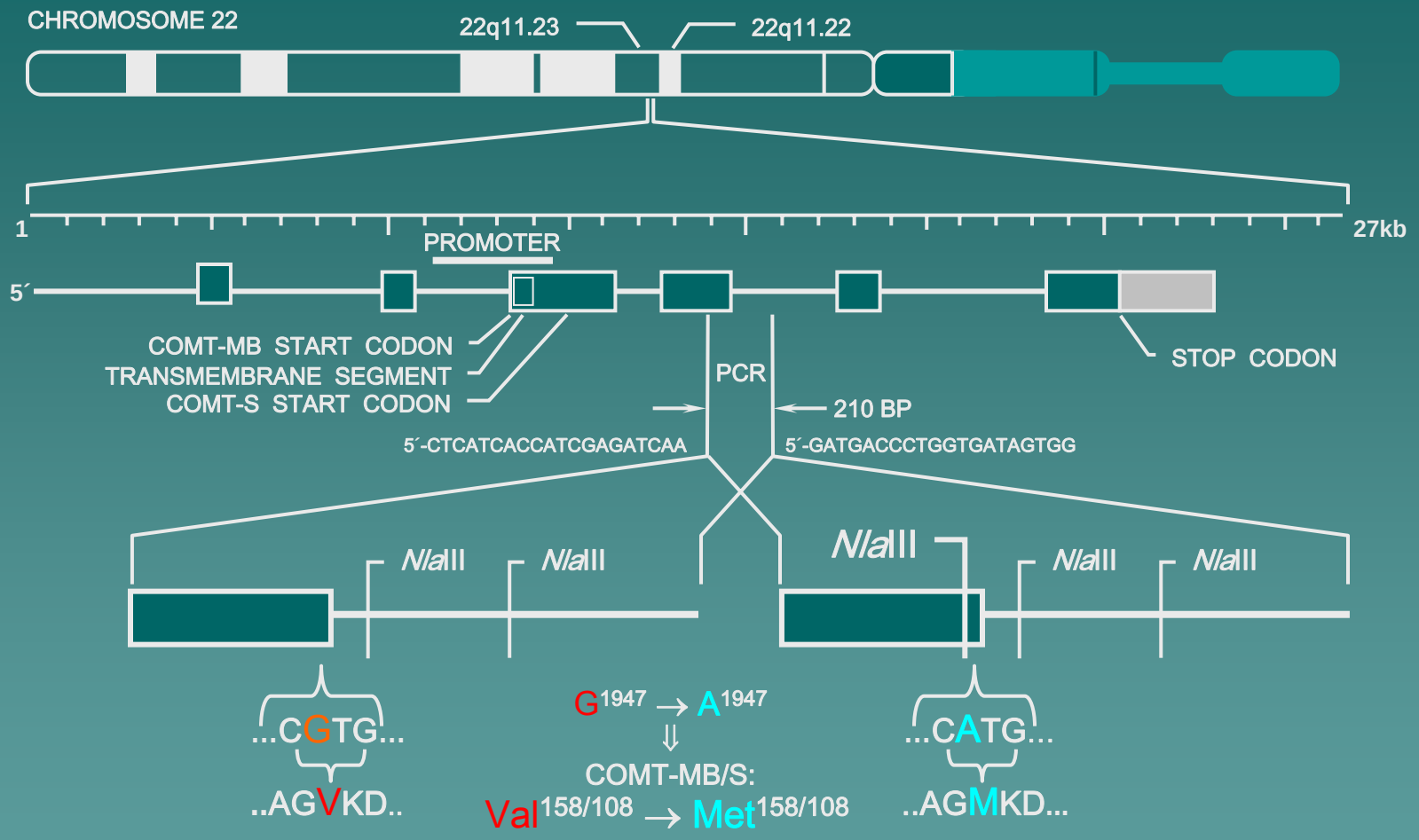
- Schizophrenia
  - **Brain illness with subtle structural and functional changes**
  - **Active area of imaging research with many competing theories and approaches**
- Progress hampered by
  - **Inconsistent data & lack of replications**
  - **Noncomparable imaging techniques**
  - **Small and diverse patient populations**

The problem

- Schizophrenia is highly heritable
- No single gene
- Believed to be:
  - Multigenetic
  - Each with a small contribution

- How do you identify the genes and determine their influence on behavior?

The COMT Gene



high-activity (3-4X)
thermo-stable
Low Dopamine Available

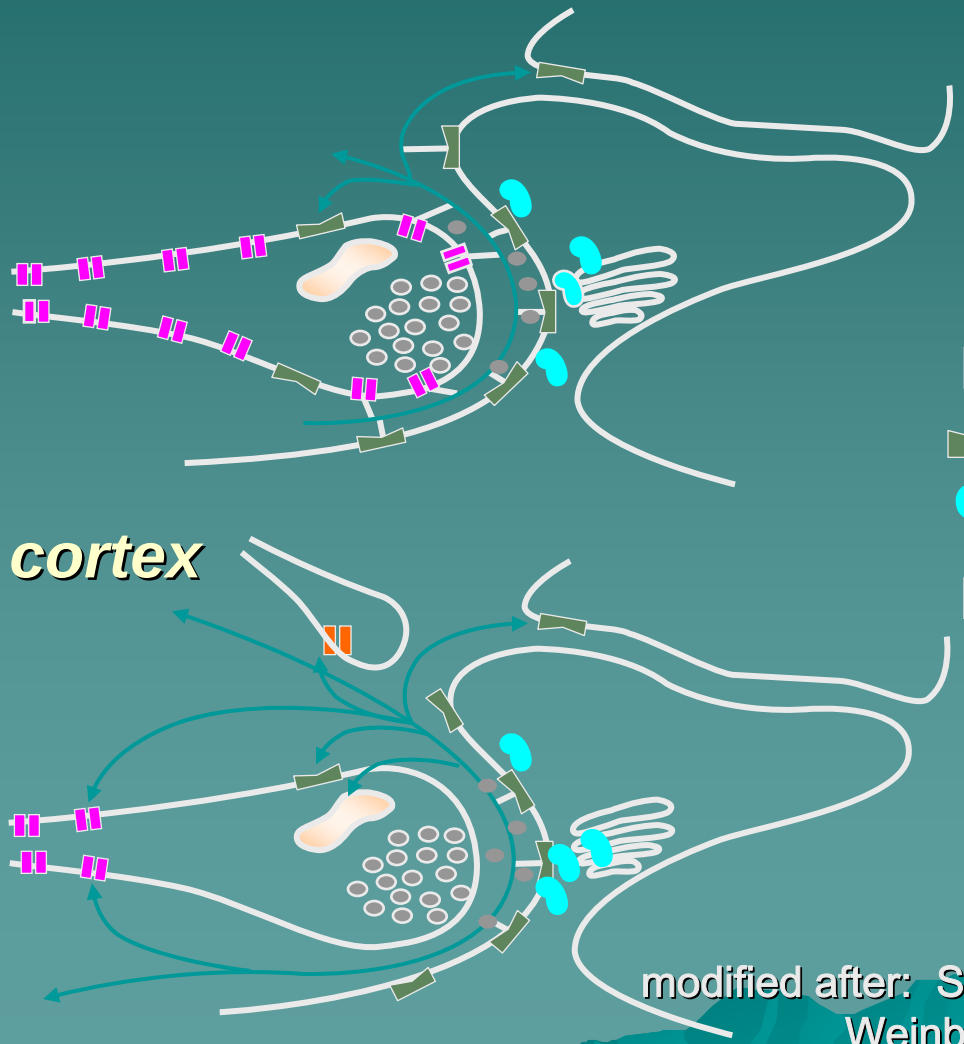
low-activity (1X)
thermo-labile
More Dopamine Available

SOURCE: NCBI, GEN-BANK, ACCESSION # Z26491

Dopamine terminals in striatum and in prefrontal cortex are not the same

Striatum

Prefrontal cortex



DA

DA transporter

DA receptor

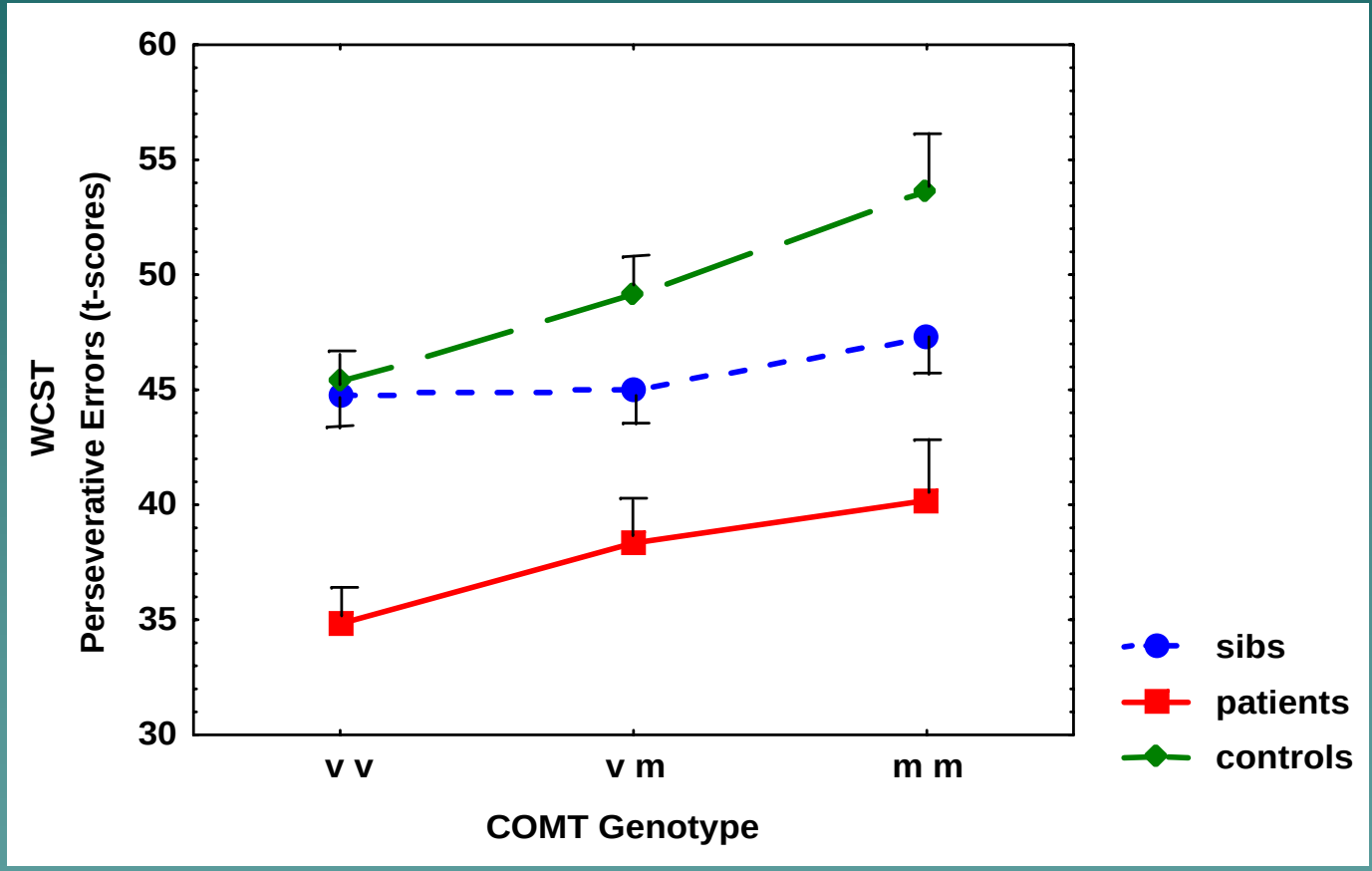
COMT

NE transporter

modified after: Sesack et al *J. Neurosci* 199

Weinberger, ICOSR, 2003

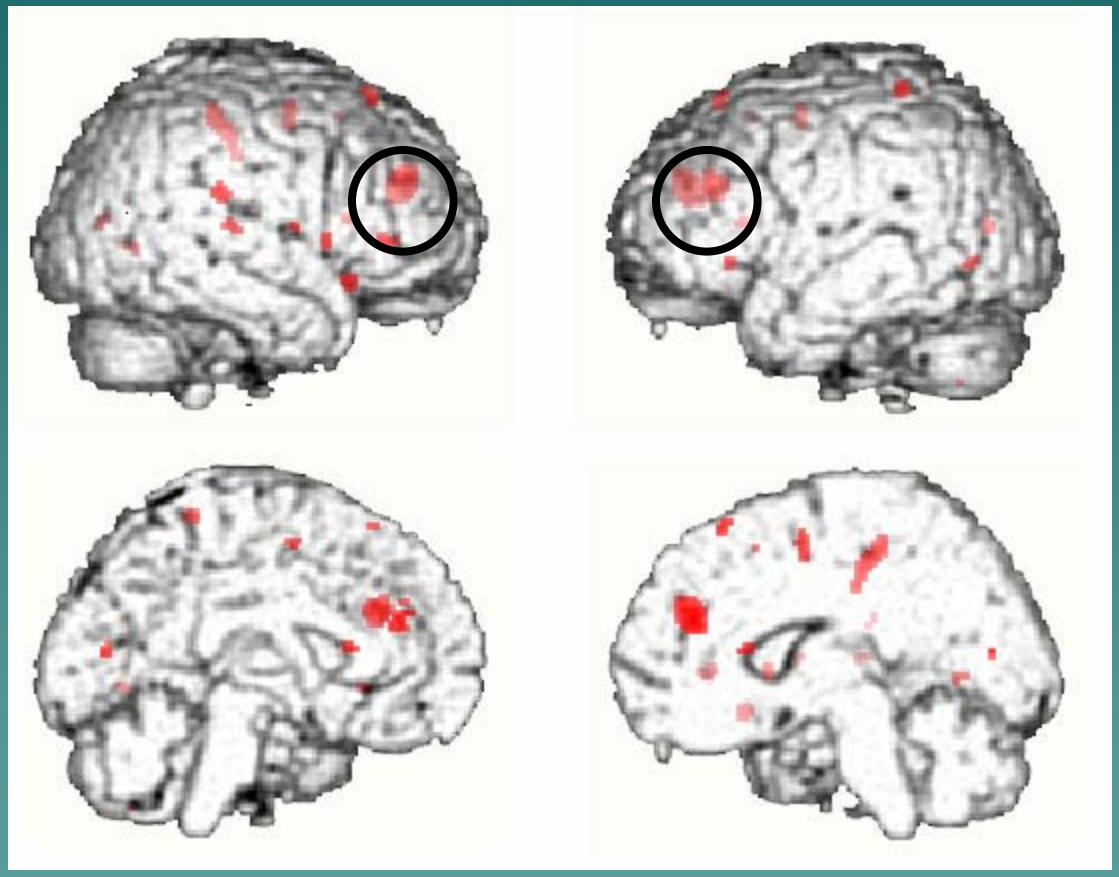
Example:
COMT Genotype Effects Executive Function



Genotype Effect (F=5.41, df= 2, 449); p<.004.

Egan et al *PNAS* 2001

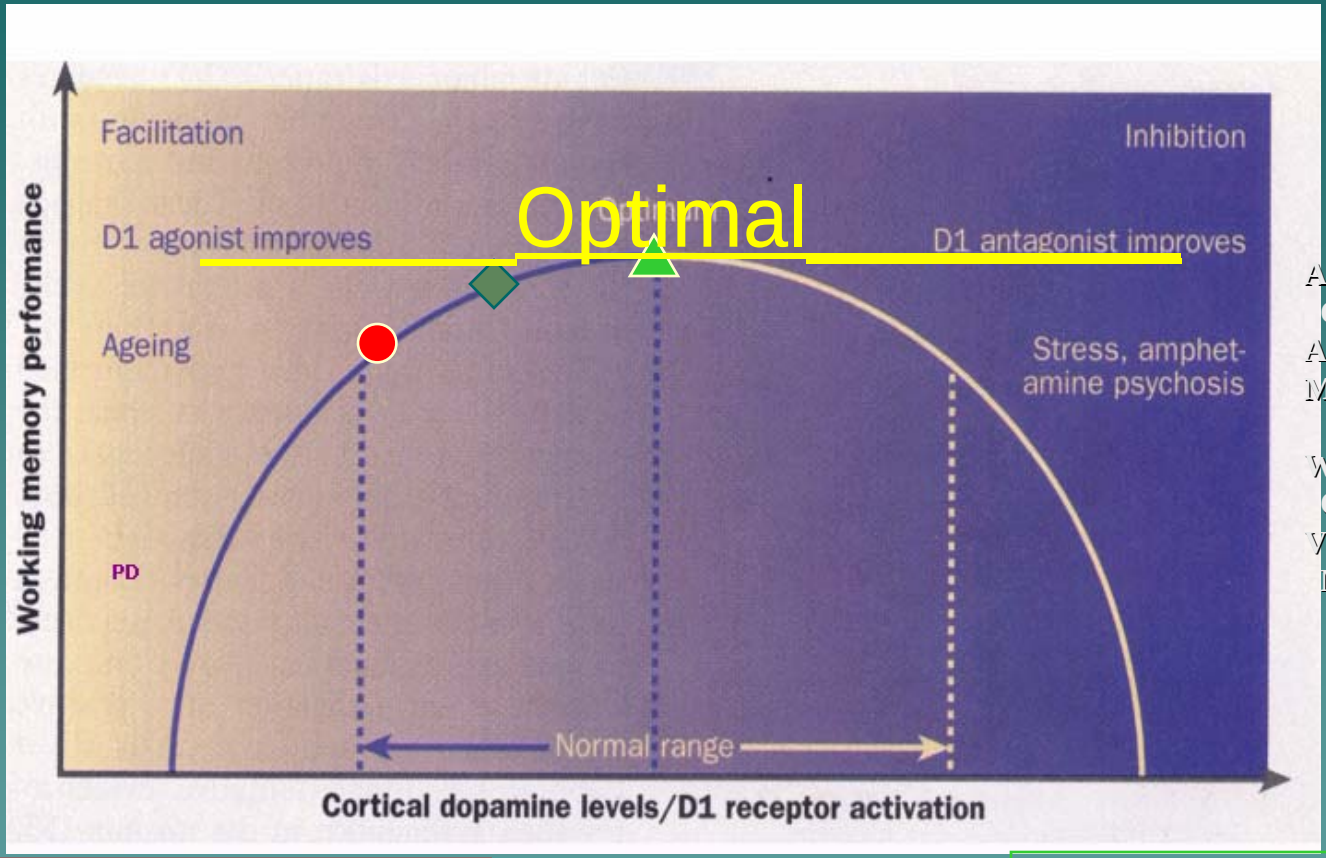
COMT Genotype and Cortical Efficiency During fMRI Working Memory Task



Val-val>val-met>met-met use more DLPFC to do same task, SPM 99, p<.005

Egan et al *PNAS* 2001

Predicted relative effects of COMT genotype on prefrontal cortical function



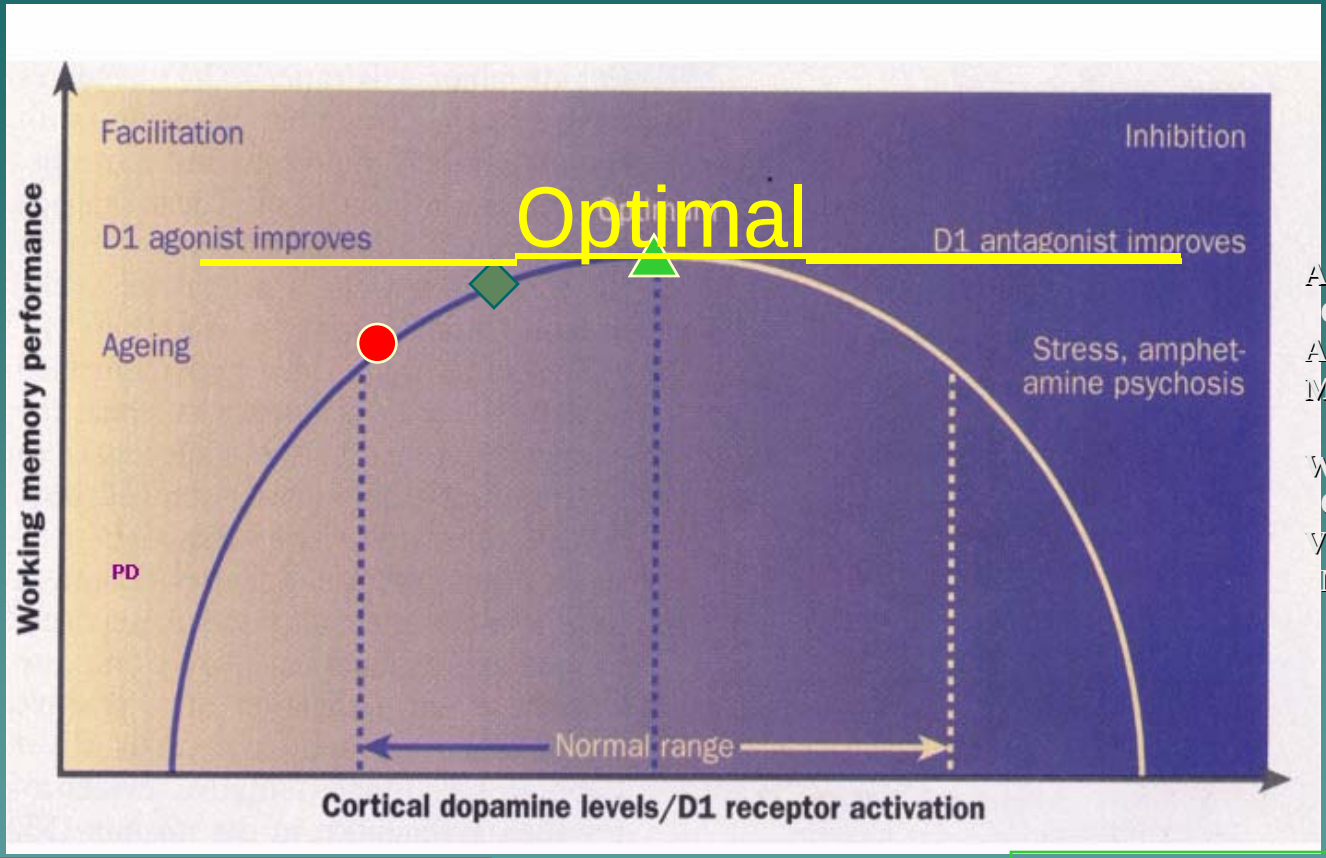
Arnsten and Goldman-Rakic, 1986
Arnsten et al., 1994
Murphy et al., 1994, 1996 a,b, 1997
Williams and Goldman-Rakic, 1995
Verma and Moghaddam, 1996

'VV' - high COMT activity
LOW synaptic dopamine

'mm' – low activity
HIGH synaptic dopamine

'vm' – intermediate

Predict that DRD1 genotype will influence prefrontal cortical function



Arnsten and Goldman-Rakic, 1986
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Williams and Goldman-Rakic, 1995
Verma and Moghaddam, 1996

'VV' - high COMT activity
LOW synaptic dopamine

'mm' – low activity
HIGH synaptic dopamine

'vm' – intermediate

Metabolic Changes with Clozapine by D1 Alleles

MHS 8

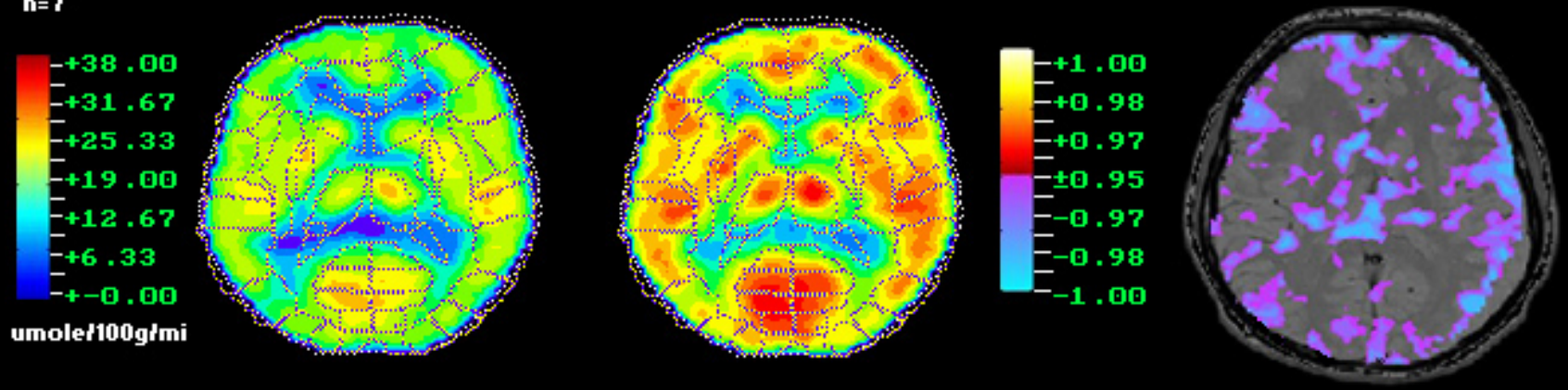
AA
Allele 22

n=7

Clozapine

Baseline

Clozapine-Baseline
BPRSpos = 30% Improvement



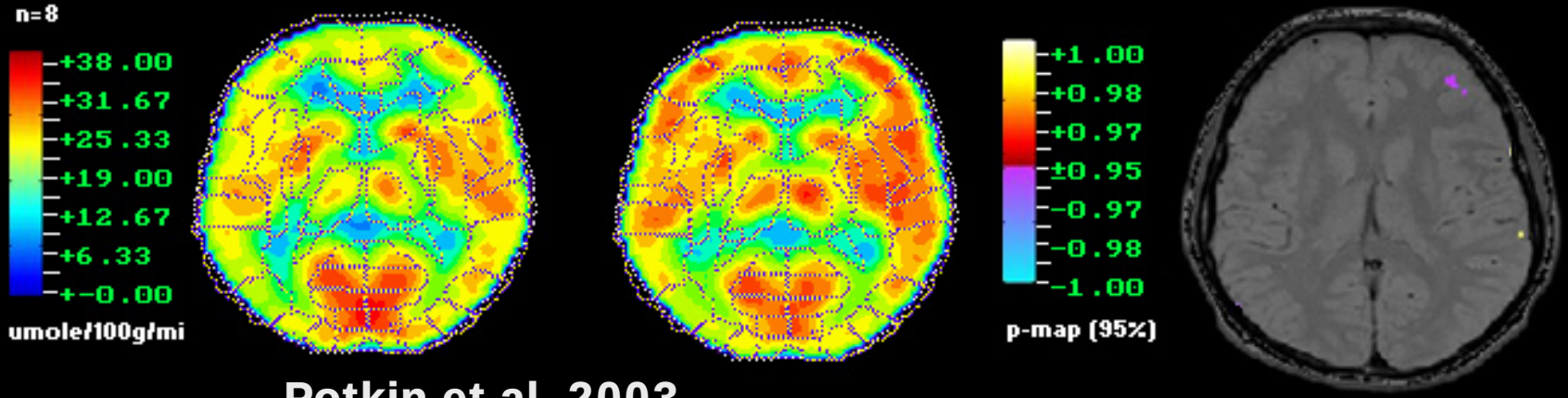
AT
Allele 12

n=8

Clozapine

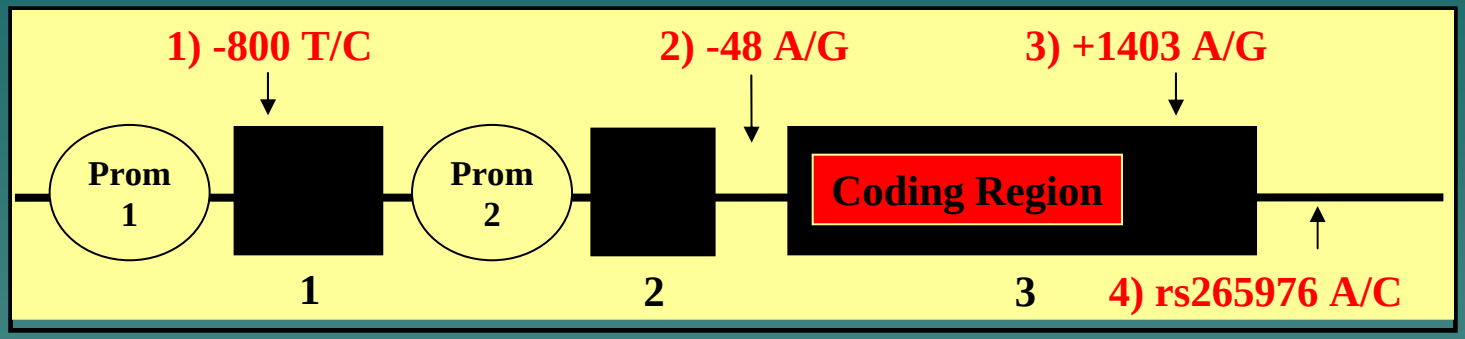
Baseline

Clozapine-Baseline
BPRSpos = 7% Worsening



Potkin et al ,2003

DRD1 Polymorphisms in Clozapine Response (N=234)



Ethnicity	Global P Value	Haplotype	Responder: n (Est. Freq.)	Non-Responder: n (Est. Freq.)	P Value
Caucasian	0.616	1-2-1-2	0.9 (0.01)	5.7 (0.02)	0.016
African-American	0.189	1-2-2-2	3.0 (0.06)	0.0 (0.00)	0.042

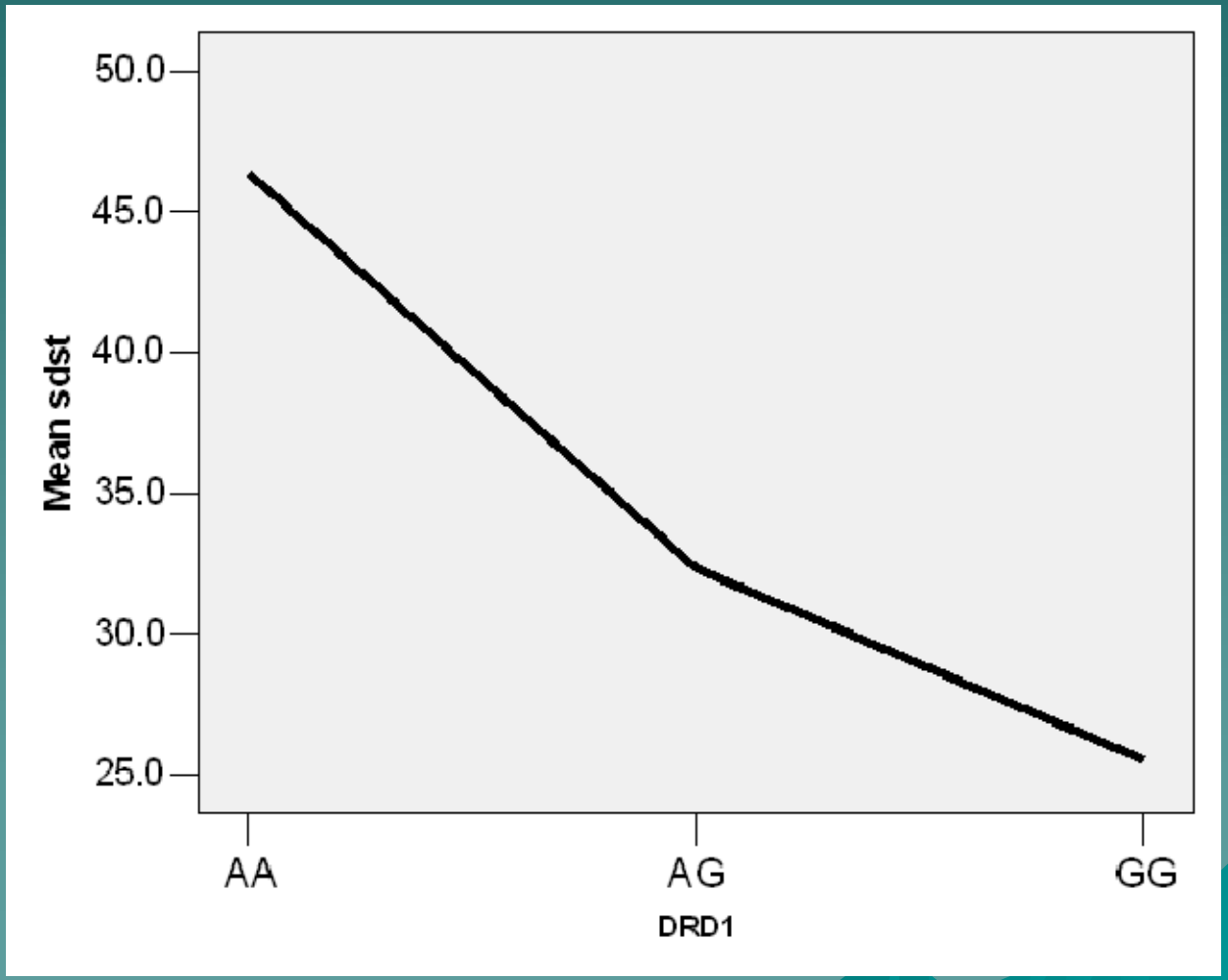
-48 G allele over represented in the non responders

Hwang, R et al ASSOCIATION STUDY OF FOUR DOPAMINE D1 RECEPTOR GENE POLYMORPHISMS AND CLOZAPINE TREATMENT RESPONSE

Attentional/WM Performance by DRD1 Genotype

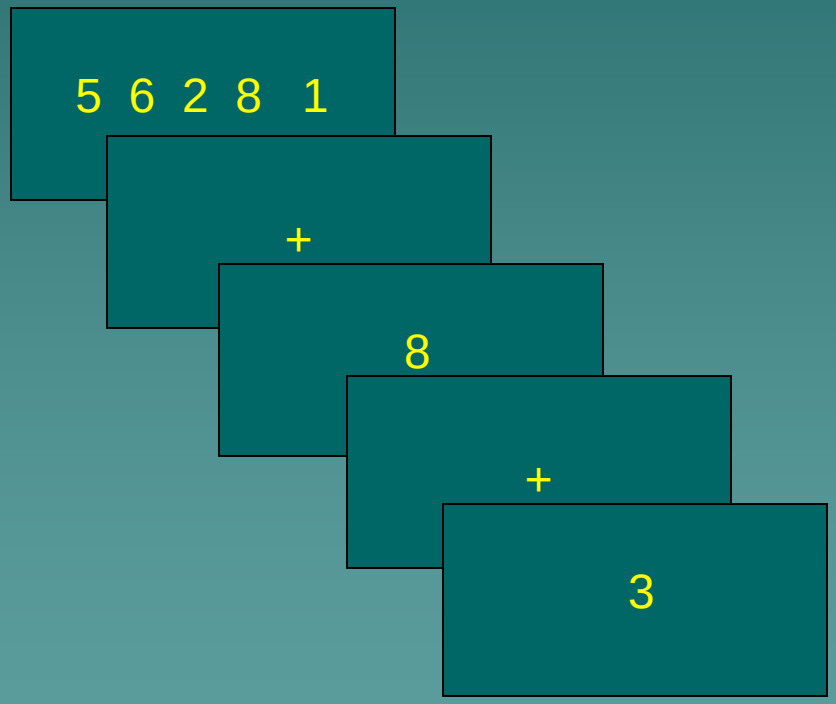
C-MINDS Battery

•Symbol Digit Substitution Test (total correct in 60 sec), p< .038

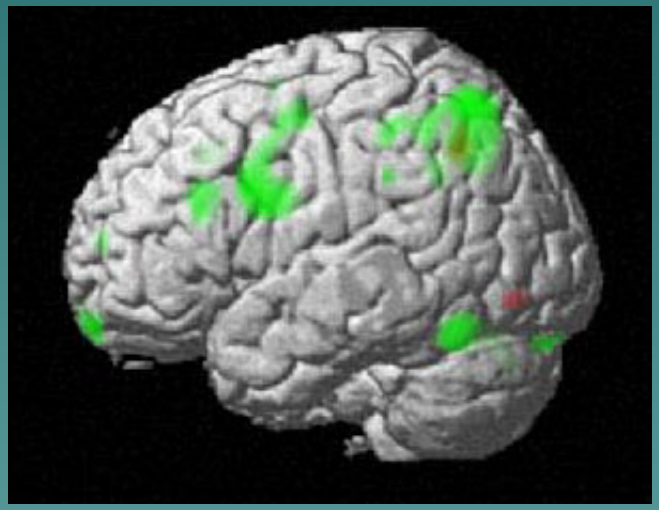


Working Memory

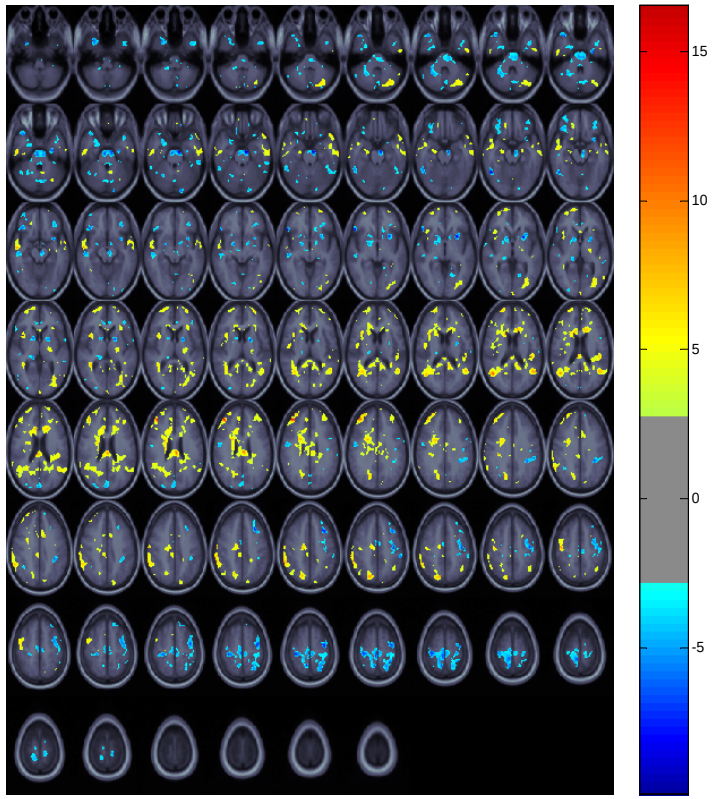
- Sternberg task:

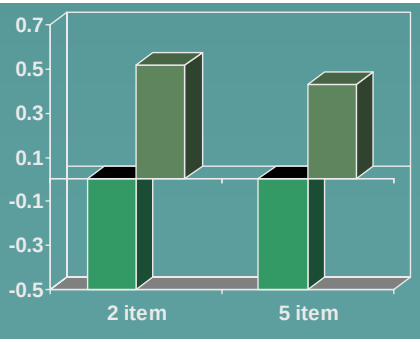


- Example Data

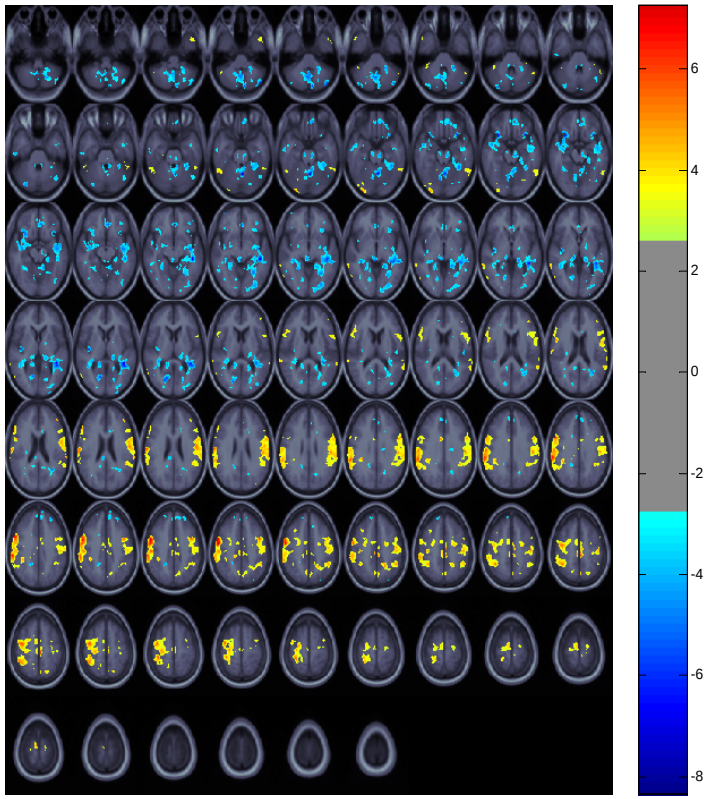


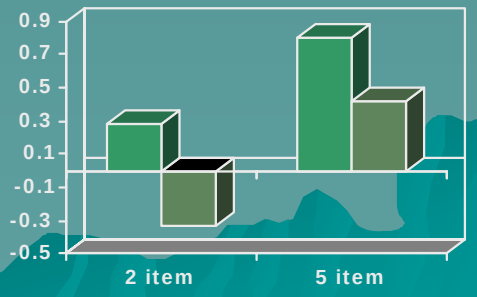
D1 Group A A





D1 Group A G

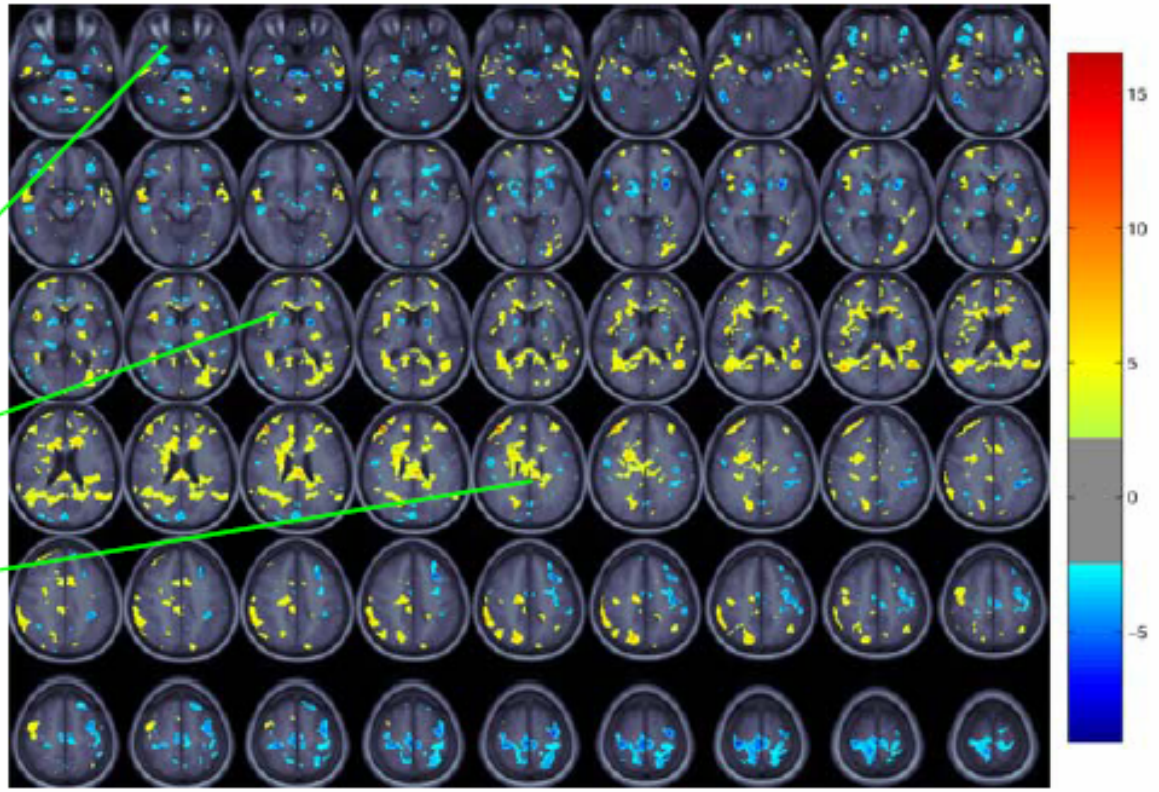


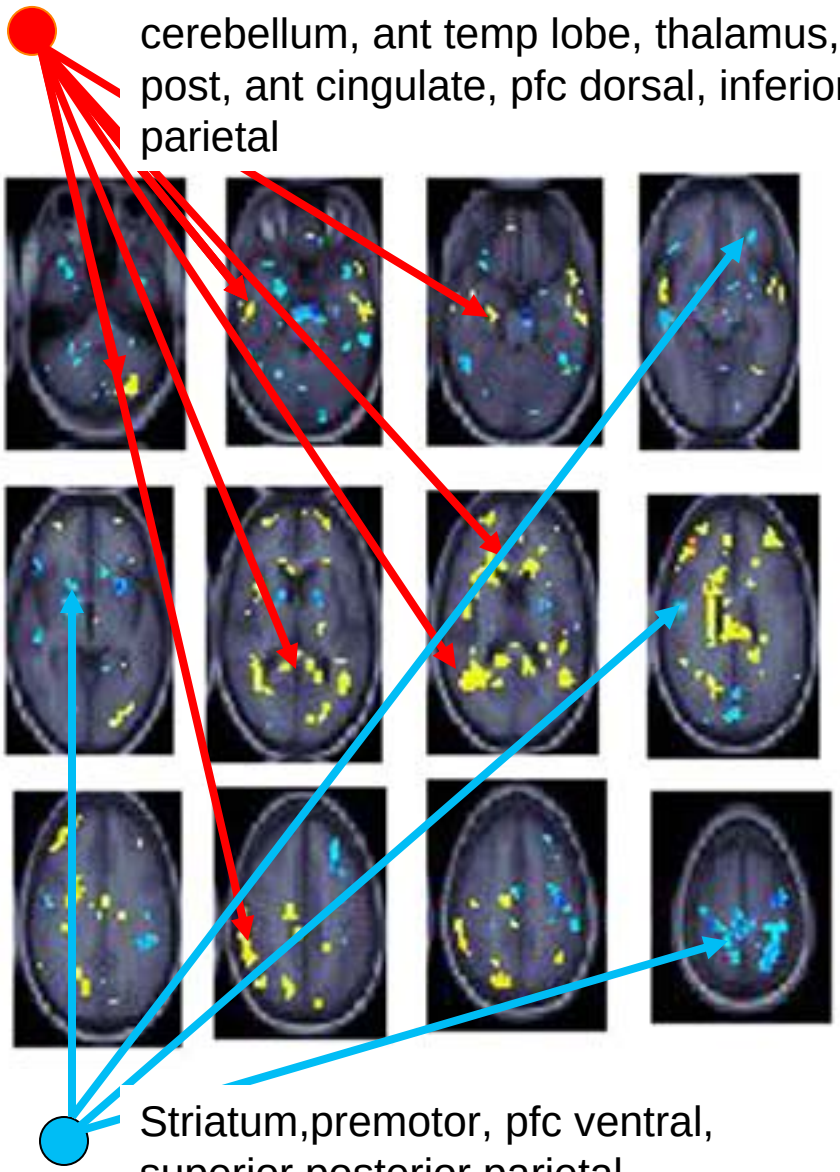


Genotype and Circuitry

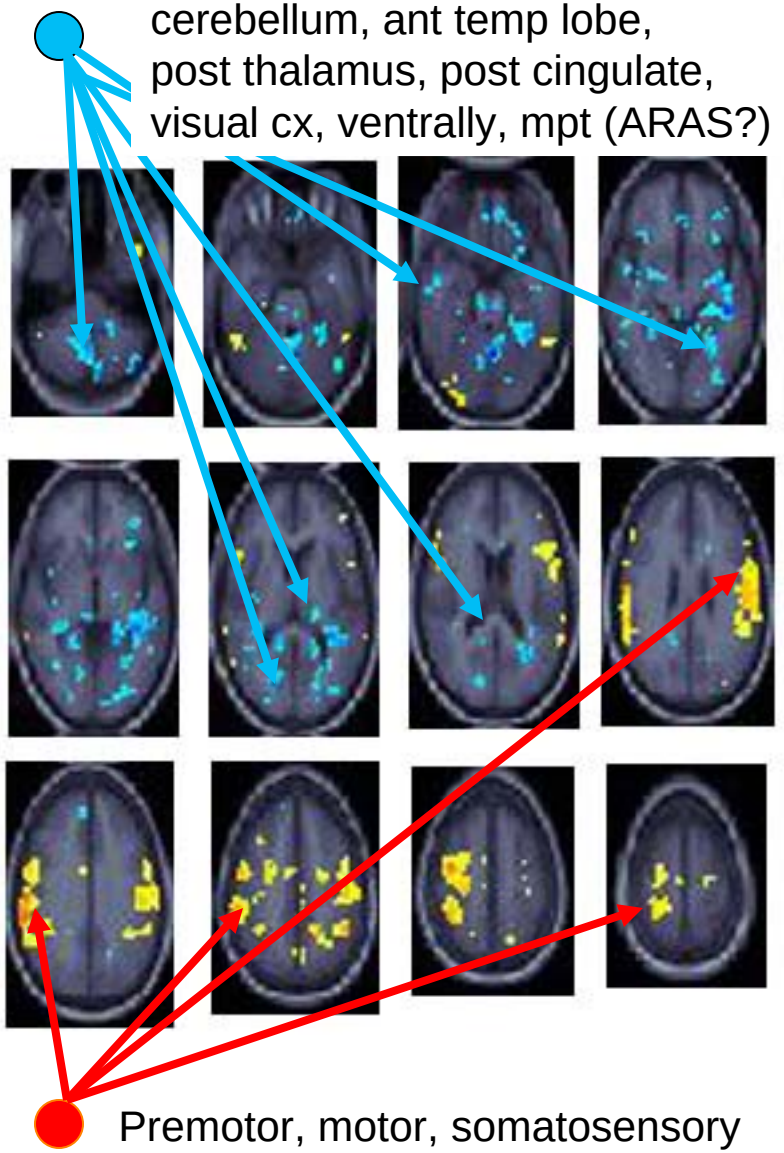
- Inverse relationship between emotion and cognition by genotype
- Method for revealing circuitry by genotype

	Low Memory Load		High Memory Load	
	Accuracy	DLPFC	Accuracy	DLPFC
Amygdala				
G1	.62	-.71	.64	-.54
G2	.08	-.43	.17	-.09
Anterior Insular				
G1	-.60	.80	-.31	.55
G2	.11	.74	-.27	.53
Cingluate Cortex				
G1	-.76	.87	-.69	.62
G2	-.33	-.05	-.10	.44





Implied circuits: cerebellar/pontine/pfc, Ant+post attentional, language; Spatial, striatal



Implied circuits: Sensorimotor, premotor; Cerebellar, ventral visual, post attentional

The limits of these approaches

- Often, it's a single gene, single measure approach
- Hypothesis-driven methods fail when faced with these datasets
  - Hundreds of thousands of SNPs
  - Thousands of measures
  - Hundreds of subjects

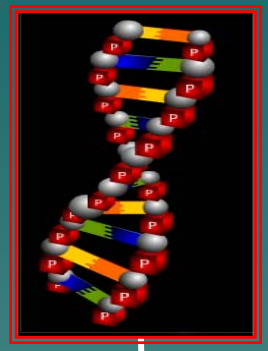
Intermediate phenotypes

Combine neuroimaging

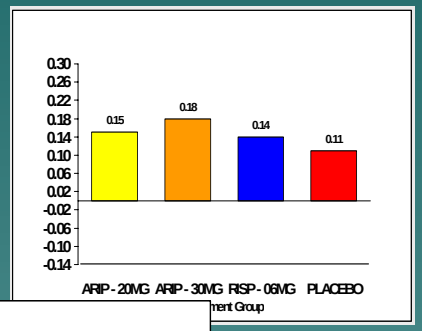
With behavioral and clinical measures

And genetics

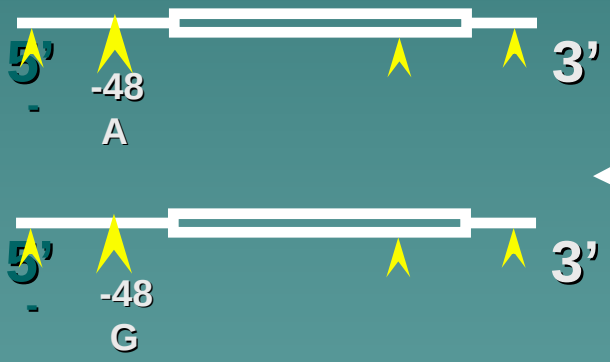
To identify useable phenotypes

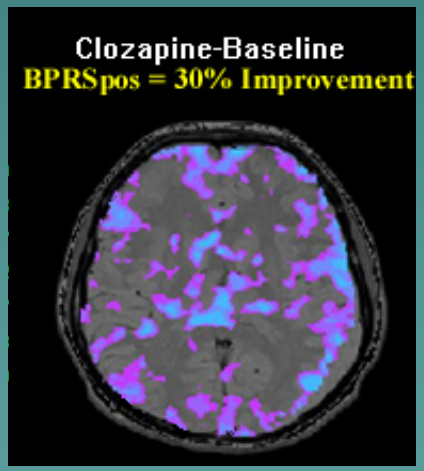


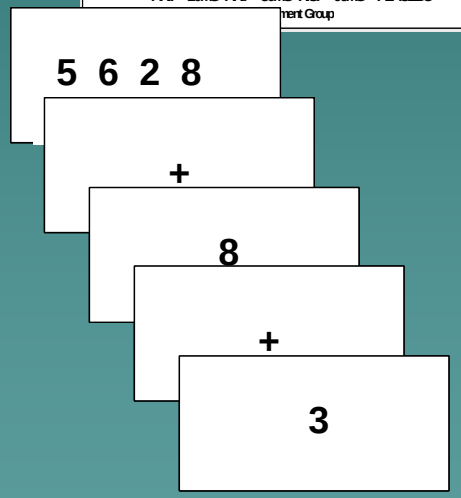
DNA



DRD1





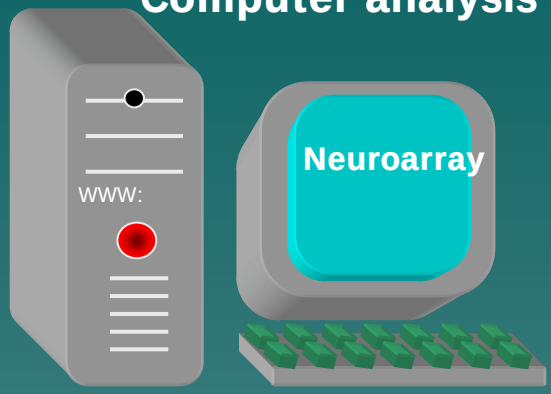


Inherited genotype

Neuroimaging

Clinical and cognitive measures

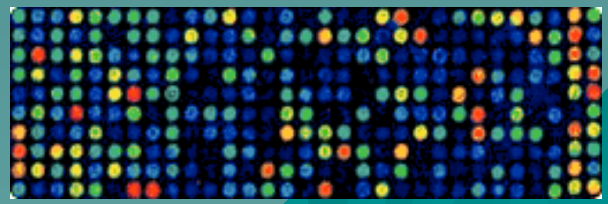
Computer analysis



Best treatment based on probabilities of medication response and development of side-effects

	Efficacy	Negative	Cognitive	DM	Weight	Suicide
Clozapine	90	80	25	50	85	2
Asenapine	90	80	50	10	15	?
Olanzapine	80	70	20	70	90	4
Ziprasidone	85	75	30	20	10	?

Analyze Image



Strategies for Discovering Novel Candidate Genes & Drug Targets in Schizophrenia

Replicated Genome Wide

Microsatellite Surveys

Identifying "Hotspots" & and Genes in ROI

Knowledge of Pathophysiology of Neuronal Circuits

Neurotransmitter Systems

Pharmacology of Disease

Candidate Genes

Microarray Screens

(30,000 Genes)

Plus validation with

In situ hybridization

Microarray Studies in Animals

Drug Models

(e.g., PCP, amphetamine)

Treatment Models

(e.g, neuroleptics)

Key principles

- Choosing the right people
  - Expertise
  - Openness to teaching, sharing, and collaborating
  - Risk-takers
- Cultural differences by disciplines
  - Creativity
  - Presentations not journals

Transdisciplinary Imaging Genetics Center
Key Investigators

William Bunney – Conte Center Director, Psychiatry
James Fallon – Neuroanatomy and Neurobiology
Yi Jin – Electrophysiology
David Keator – Bioinformatics
James Kennedy – Psychiatric genetics
Falko Keuster – Virtual reality and visualization
Fabio Macciardi – Genetics, Epidemiology, Statistics
Steven Potkin – TIGC PI, Brain imaging, psychiatry
Jessica Turner – fMRI and Cognitive Sciences
Padhraic Smyth – Computer Sciences, Datamining
Hal Stern – Statistics

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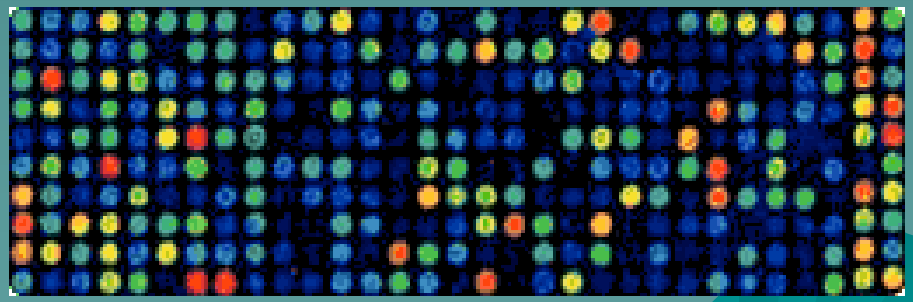
Key Investigators

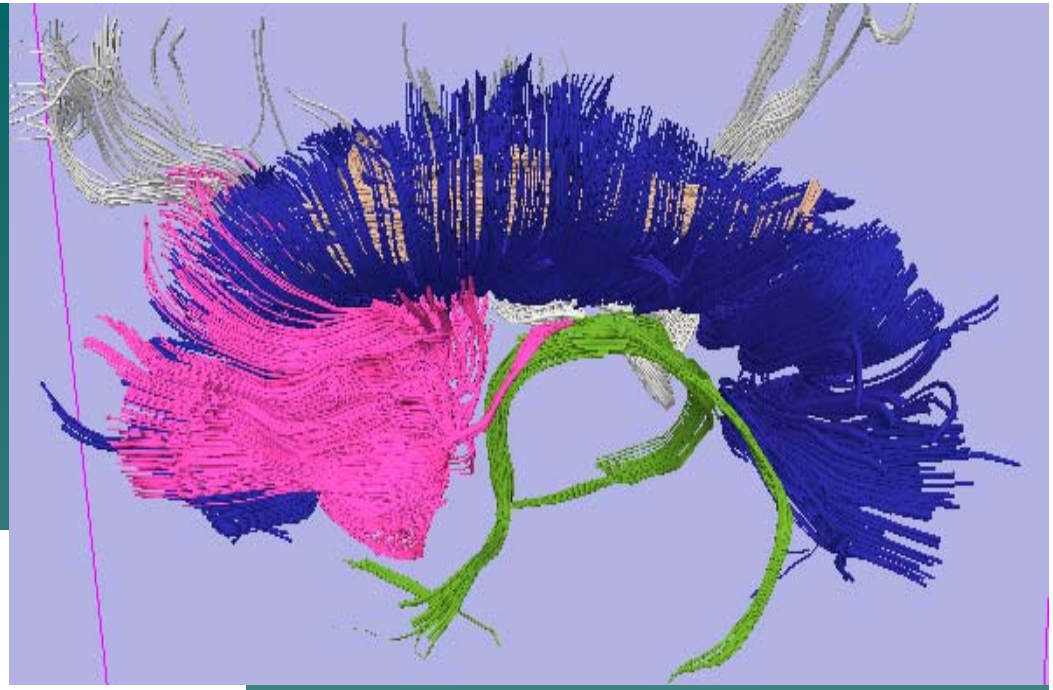
William Bunney – Conte Center Director, Psychiatry

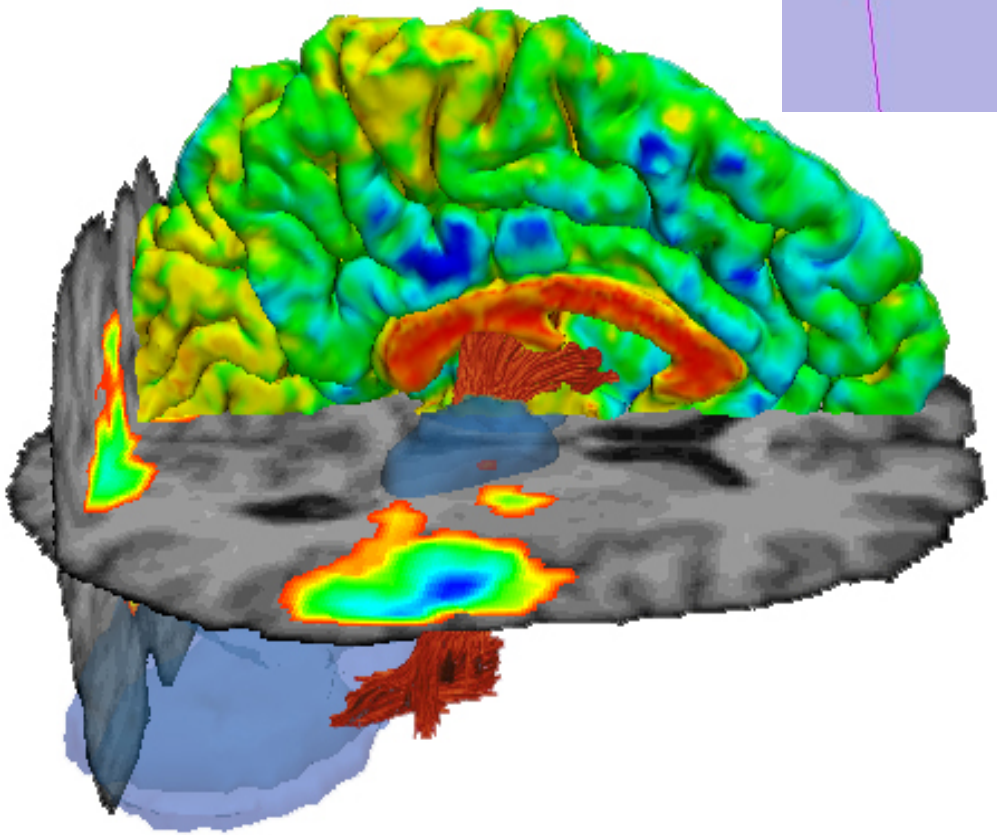
Microarray Research



TIGC

Jim Fallon Neuroanatomy

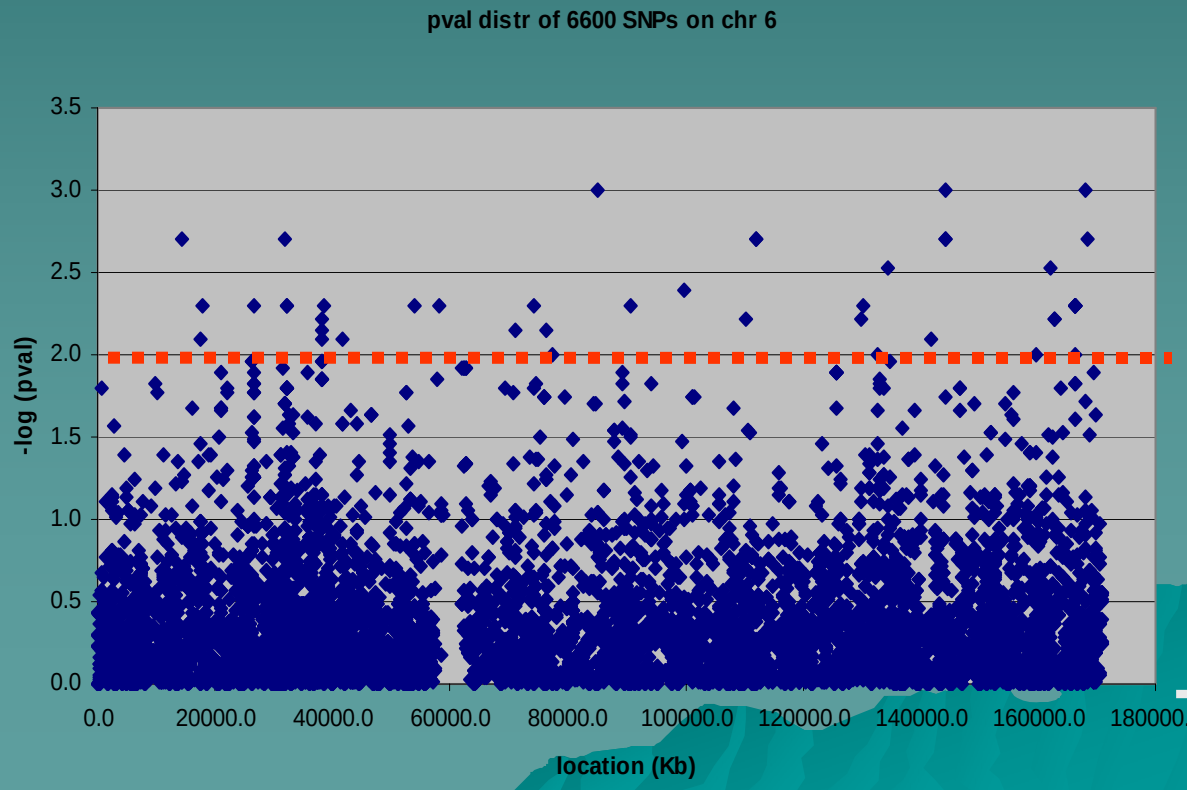




Transdisciplinary Imaging Genetics Center Key Investigators

James Kennedy – Psychiatric genetics

Fabio Macciardi – Genetics, Epidemiology, Statistics



TIGC

Transdisciplinary Imaging Genetics Center
Key Investigators

David Keator – Bioinformatics

fMRI Scanner

FMRI Images

Local File System

SRB SM = Local SM

SRB BH = Local BH

SRB AO = Local AO

SRB SIRP = Local SIRP

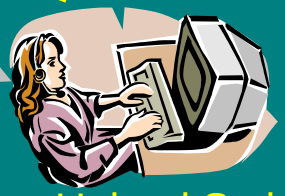
SRB

HIDB

Which Project?

Which Subject?

Which Visit?



Run Upload Script

URL Link

- ***Clinical Data***
- Computer Aided Scale Input (CALM/GAME)
- Clinical Data Entry Interface

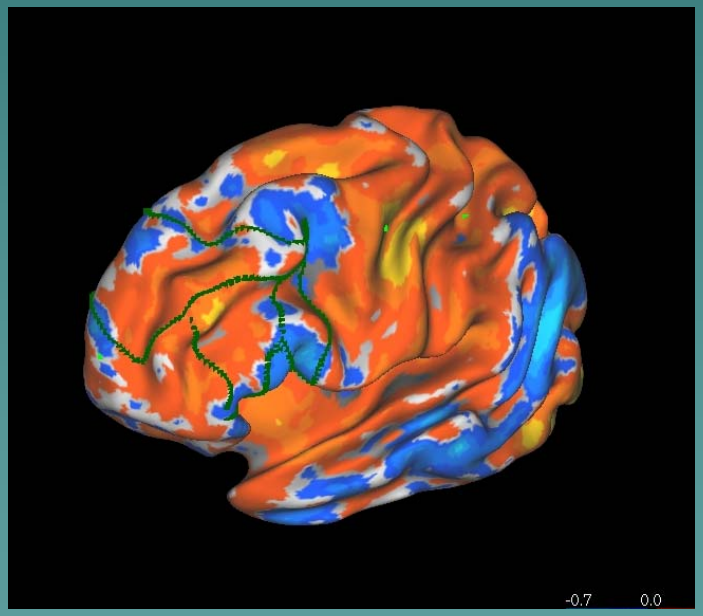
Transdisciplinary Imaging Genetics Center Key Investigators

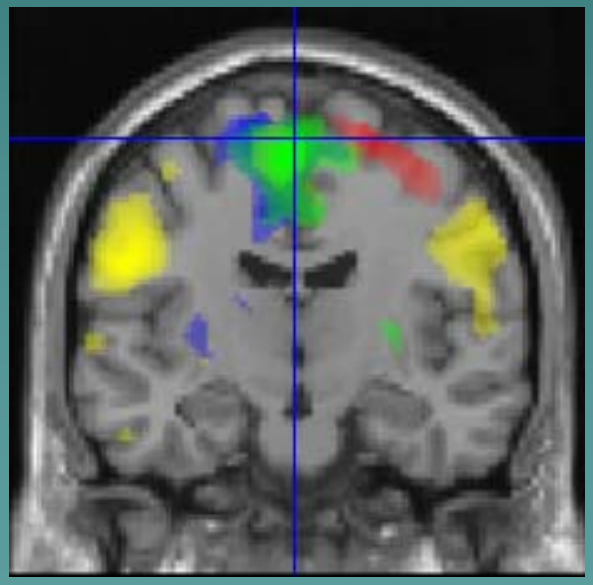
Falko Kuester – Virtual reality and visualization

TIGC

Transdisciplinary Imaging Genetics Center
Key Investigators

Jessica Turner – fMRI and Cognitive Sciences



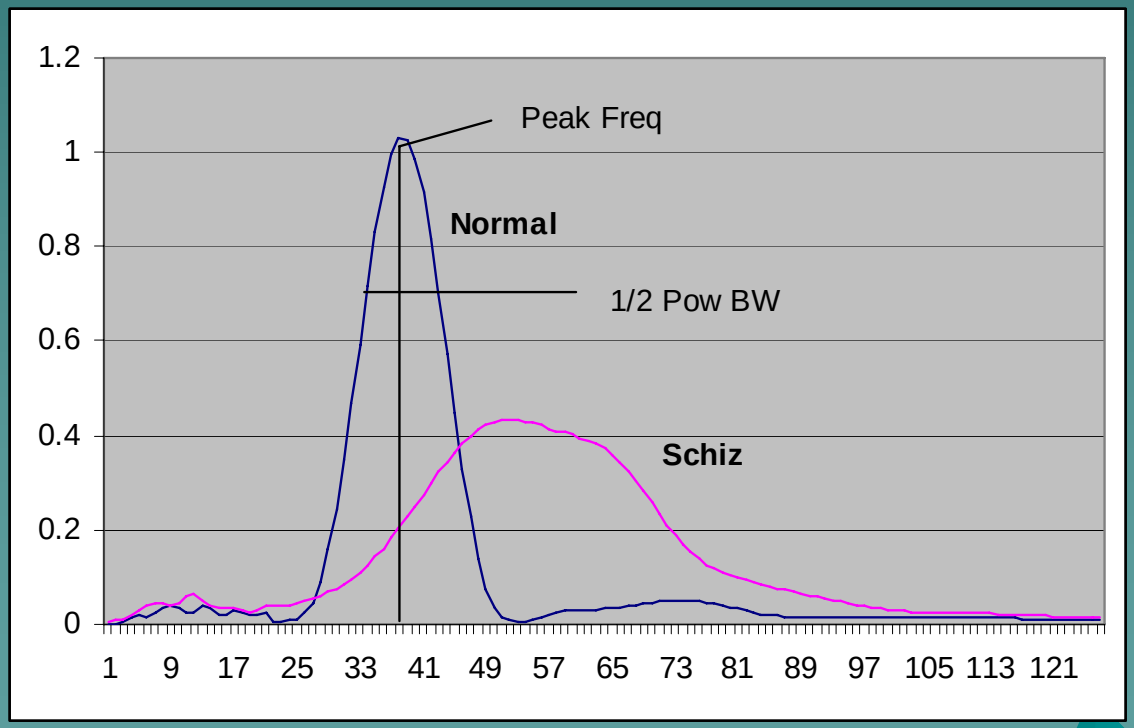


Left Wrist
Right Foot
Tongue
Left Foot

TIGC

Transdisciplinary Imaging Genetics Center
Key Investigators

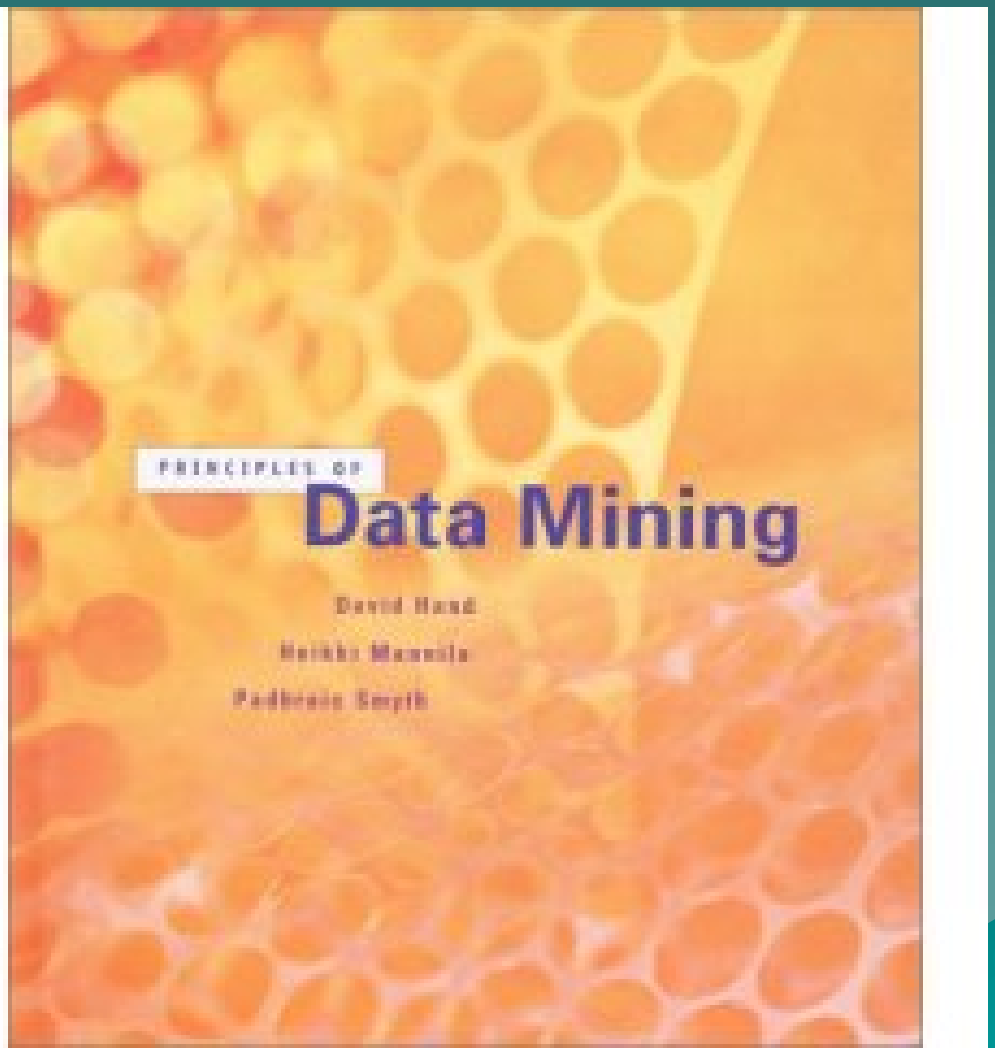
Yi Jin – Electrophysiology



TIGC

Transdisciplinary Imaging Genetics Center
Key Investigators

Padhraic Smyth – Computer Sciences, Datamining



TIGC

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Key Investigators

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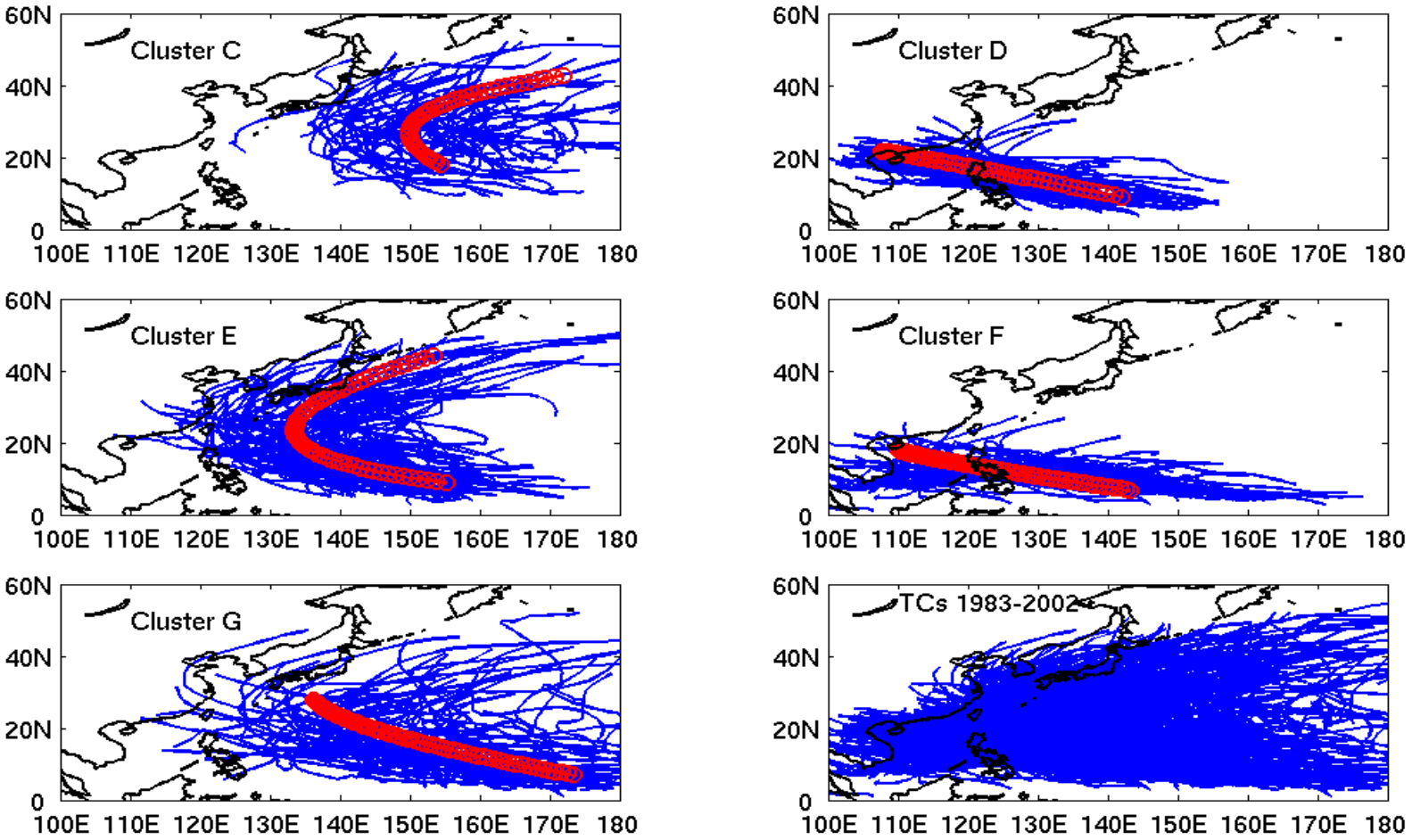


TROPICAL CYCLONES Western North Pacific 1983-2002

Transdisciplinary Imaging Genetics Center
Post-doctoral researchers and students

Imaging and genetics

Martina Panzenboeck, M.D.—imaging analyses of DTI
David Medina Fuentes, M.D.—imaging and genetics analyses
Sergey Kirshner, Ph.D.—mixture models of imaging genetic data
Seyoung Kim (Ph.D. candidate)—cluster analyses of imaging data

Genetics

Rudi Hwang, M.D.—gene-gene interactions
Clement Zai, Ph.D.—genetic polymorphisms

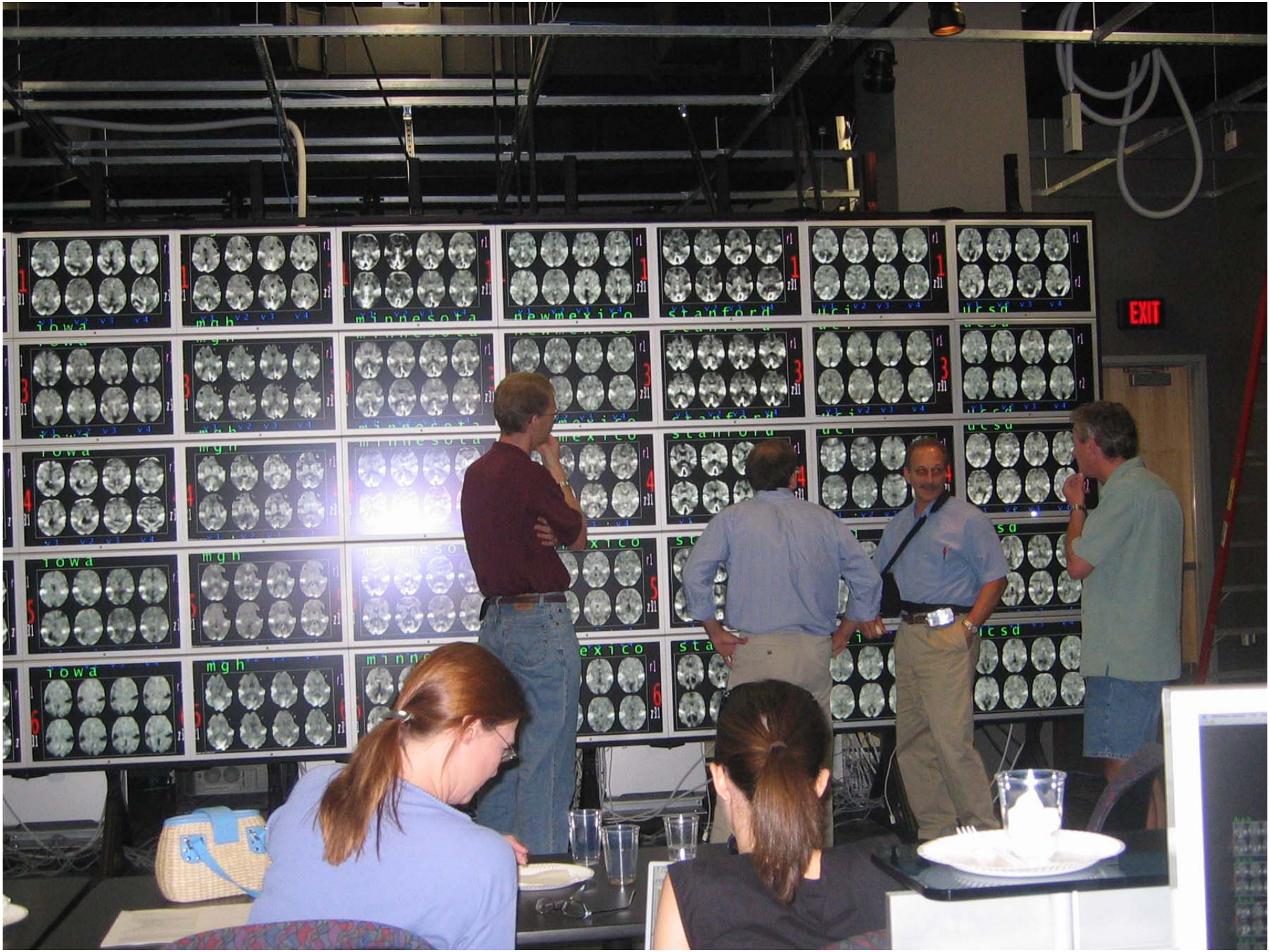
Visualizations

Vid Petrov (Ph.D. candidate)—visualization of imaging data
Zhiyu He (Ph.D. candidate)—visualization of cluster data

TIGC

Establish a common language

- Didactic seminars
- Weekly meetings for senior investigators

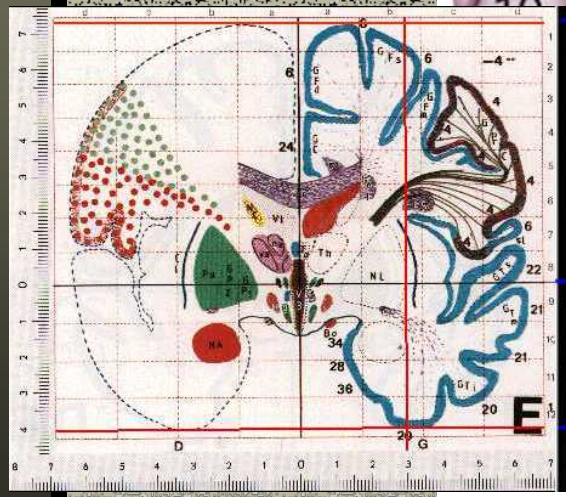

EXIT

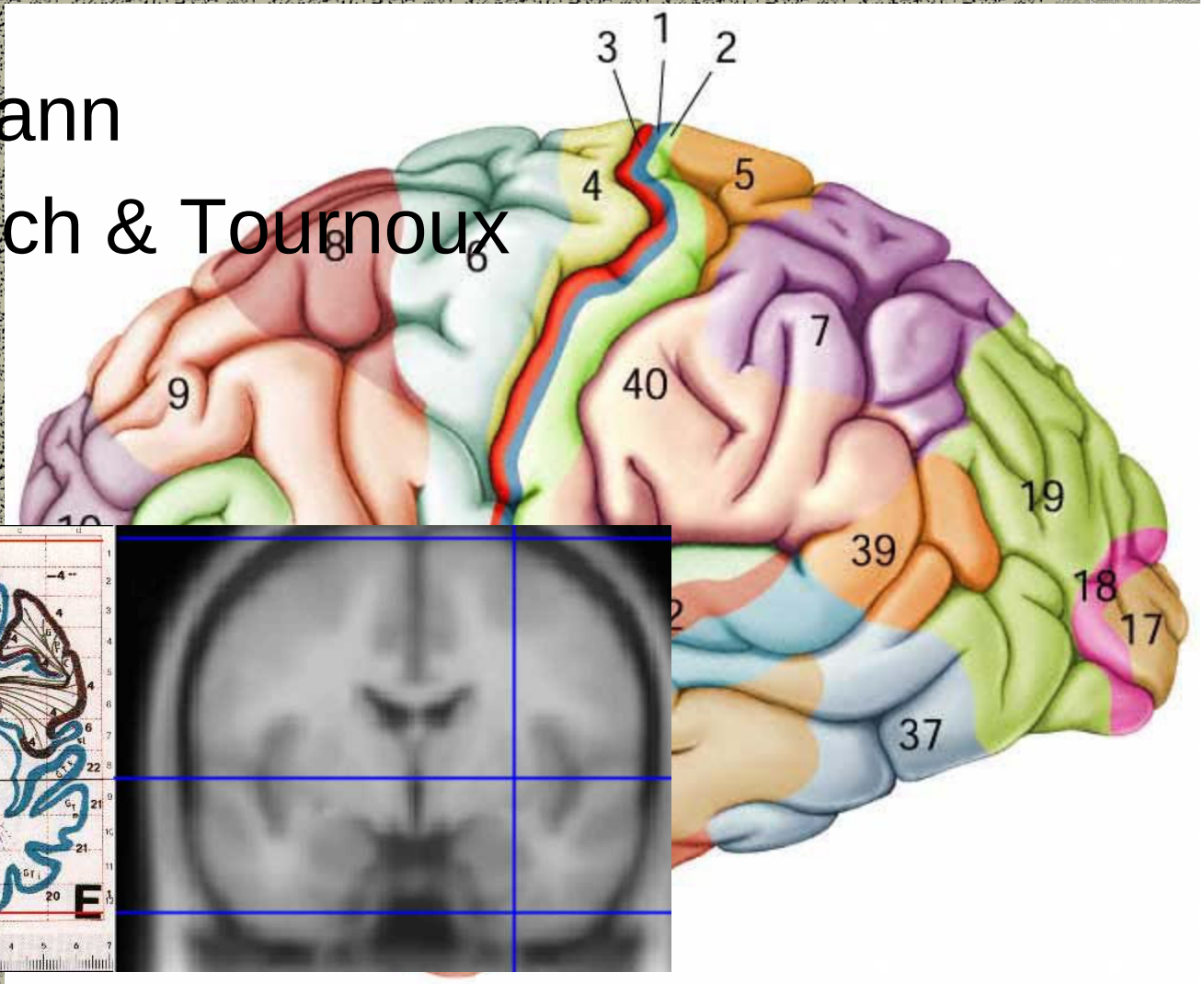
Communication

- **Introductory lectures across fields**
- MRI
- PET
- Neuroanatomy
- Clustering
- Hierarchical models
- Genetics

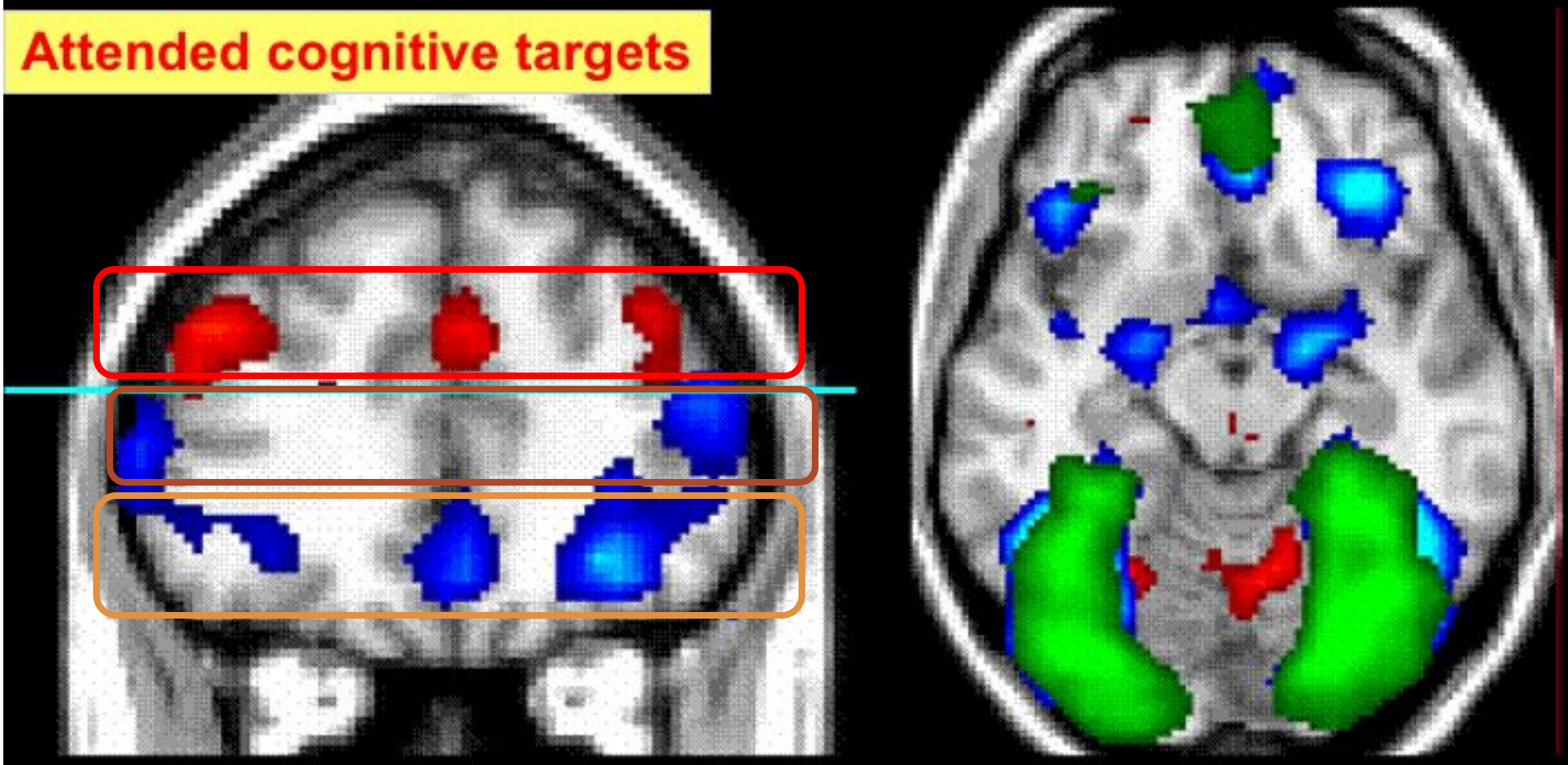
Atlases and Nomenclature

- Brodmann
- Talairach & Tournoux
- MNI
- Others



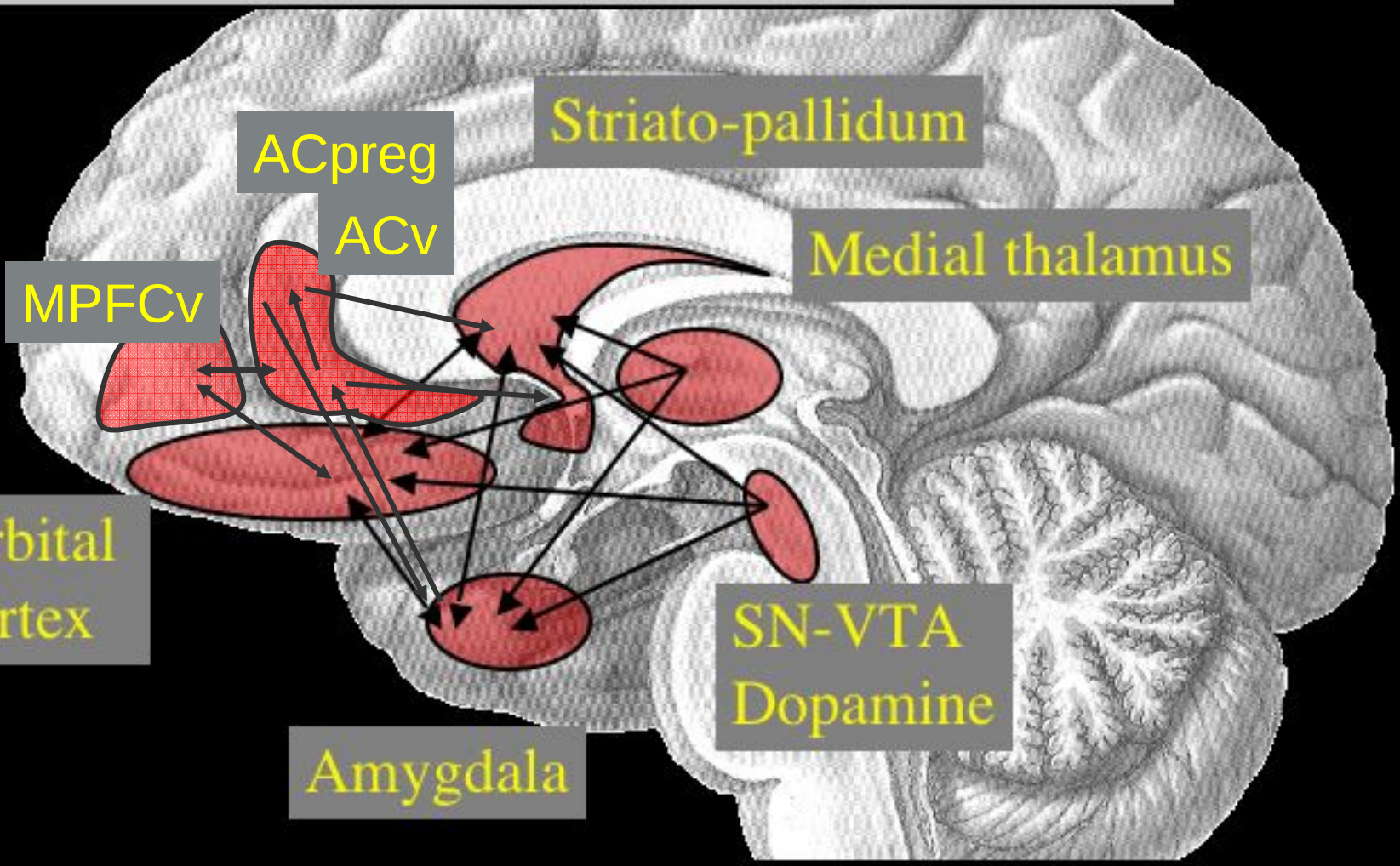


Dorsal vs ventral stream activation- fMRI



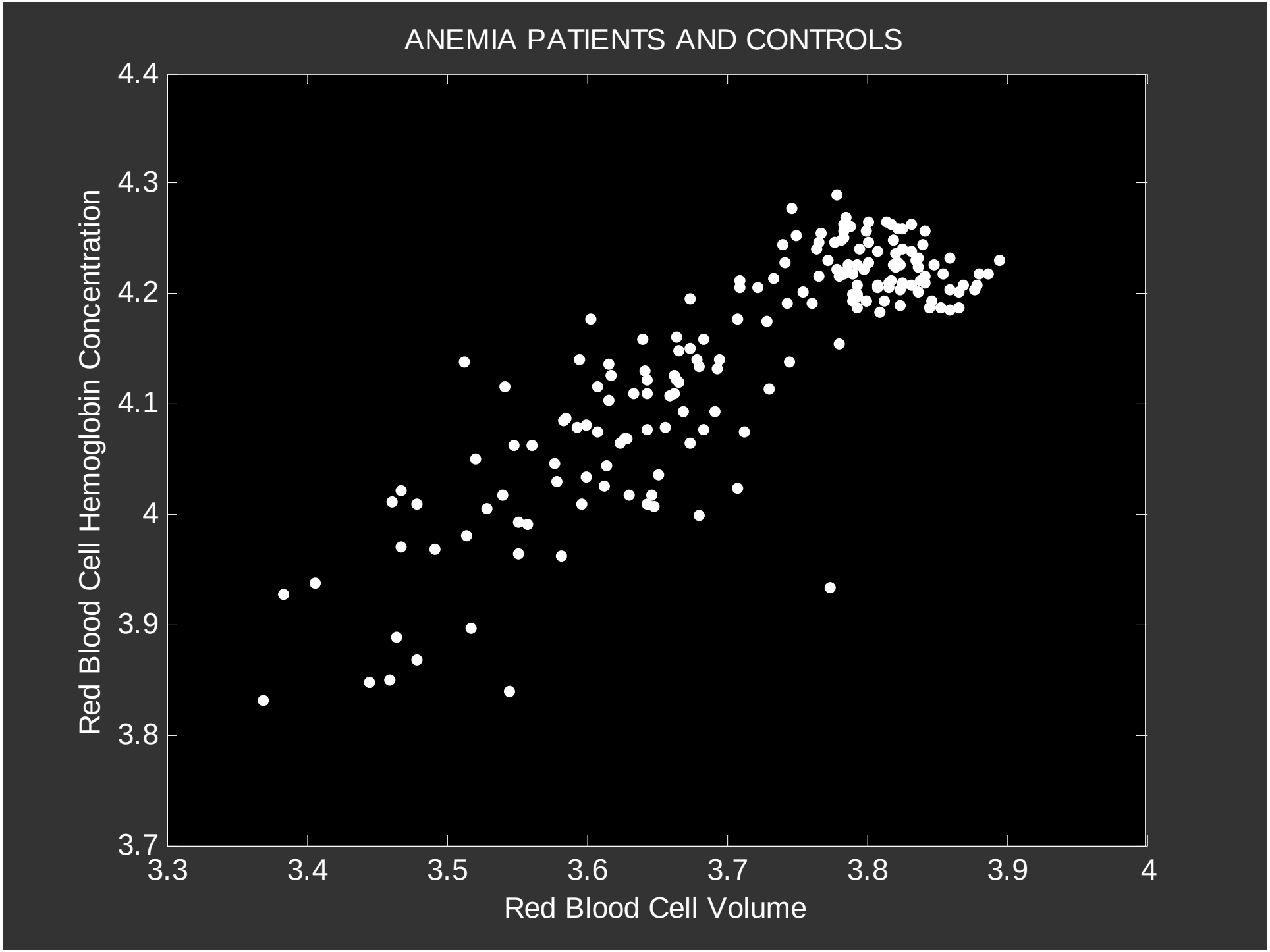
Greg McCarthy, 2004

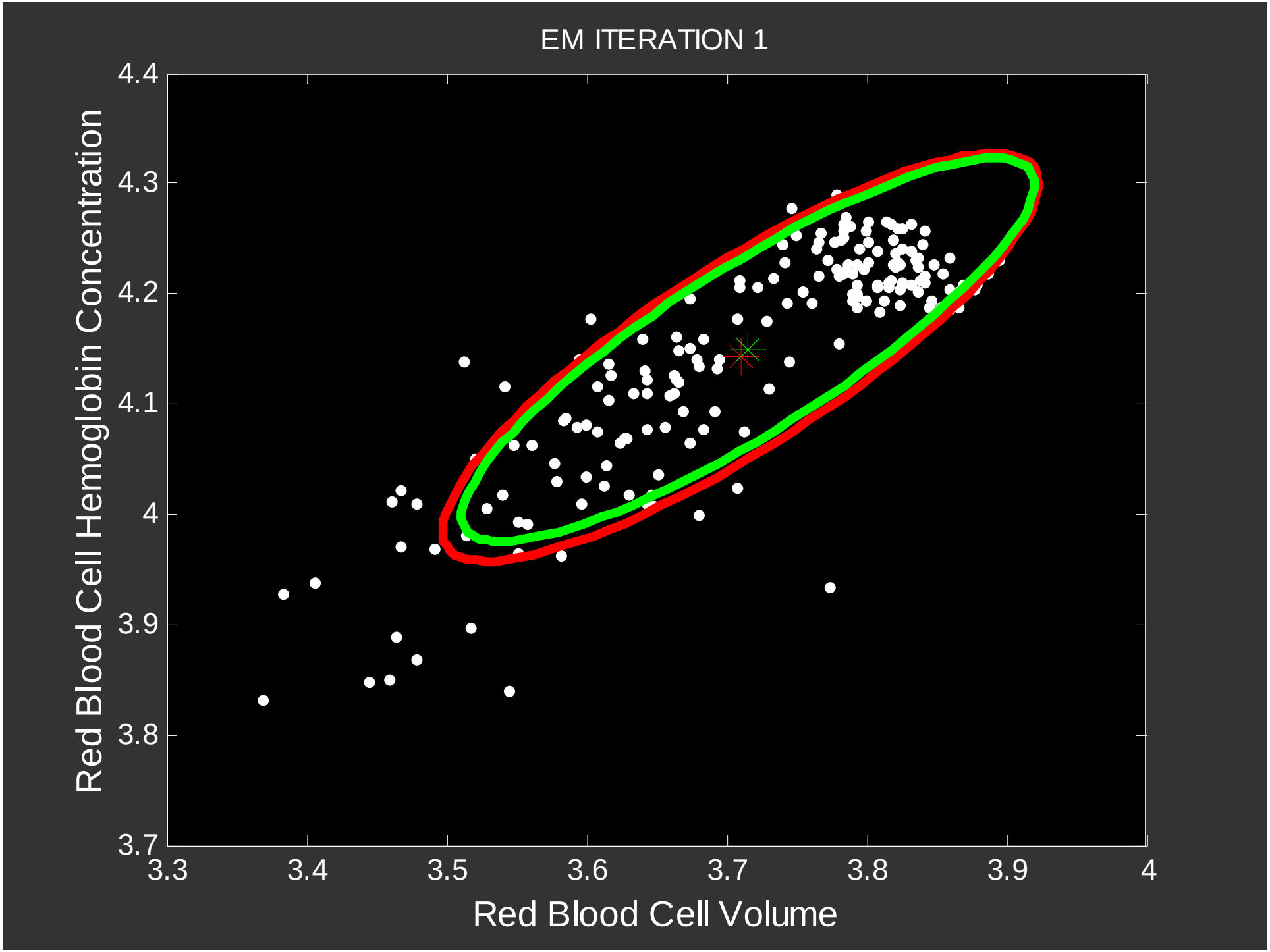
The "Ventral Prefrontal System"

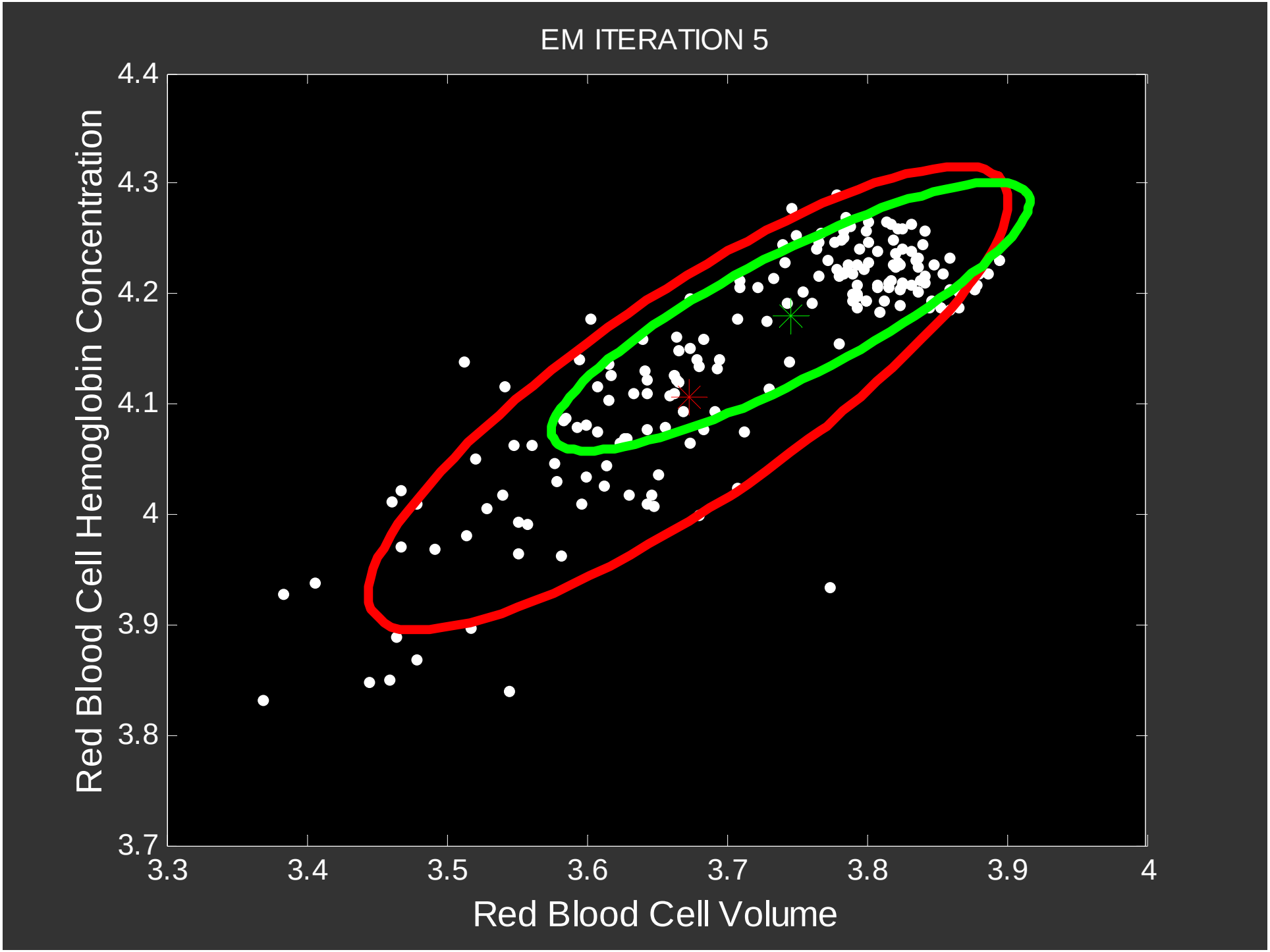


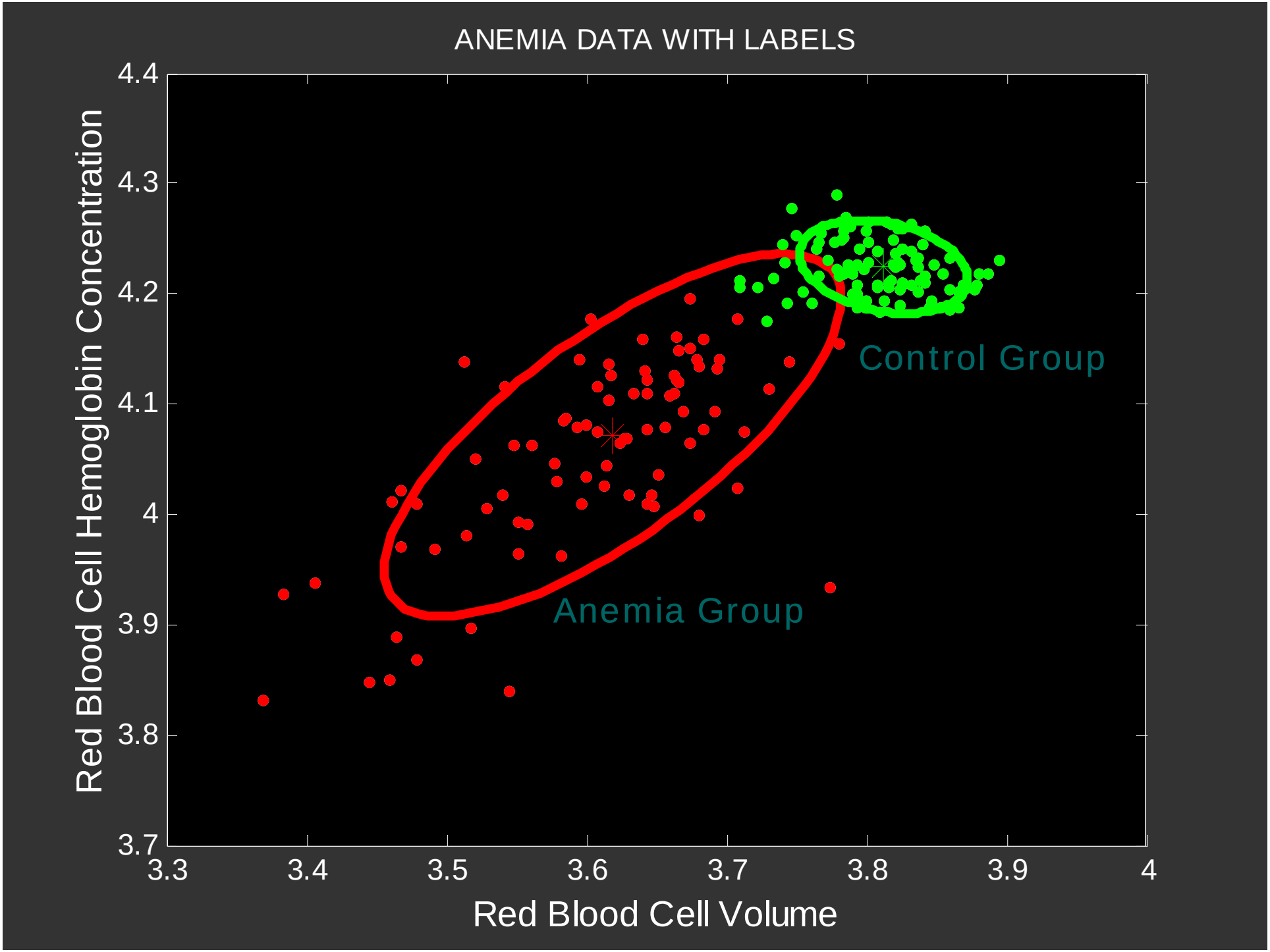
DA in the mesolimbic, mesocortical,and mesostriatal components of the"Prefrontal System"-control system for integration of emotion, motivation, will, action, and thought

Fallon

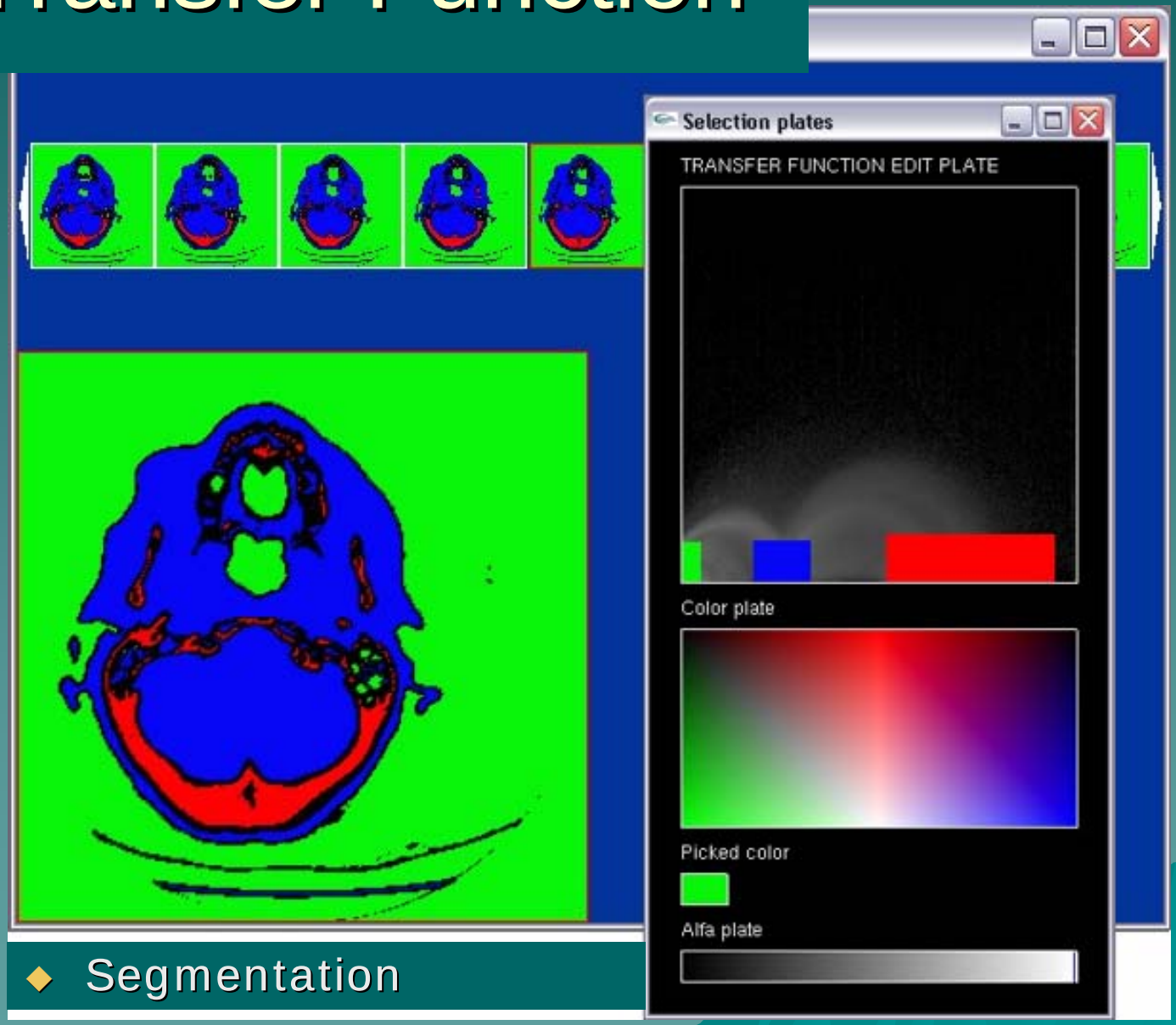

ANEMIA PATIENTS AND CONTROLS
Red Blood Cell Hemoglobin Concentration
Red Blood Cell Volume
4.4
4.3
4.2
4.1
4
3.9
3.8
3.7
3.3
3.4
3.5
3.6
3.7
3.8
3.9
4


EM ITERATION 1
Red Blood Cell Hemoglobin Concentration
Red Blood Cell Volume
4.4
4.3
4.2
4.1
4
3.9
3.8
3.7
3.3
3.4
3.5
3.6
3.7
3.8
3.9
4

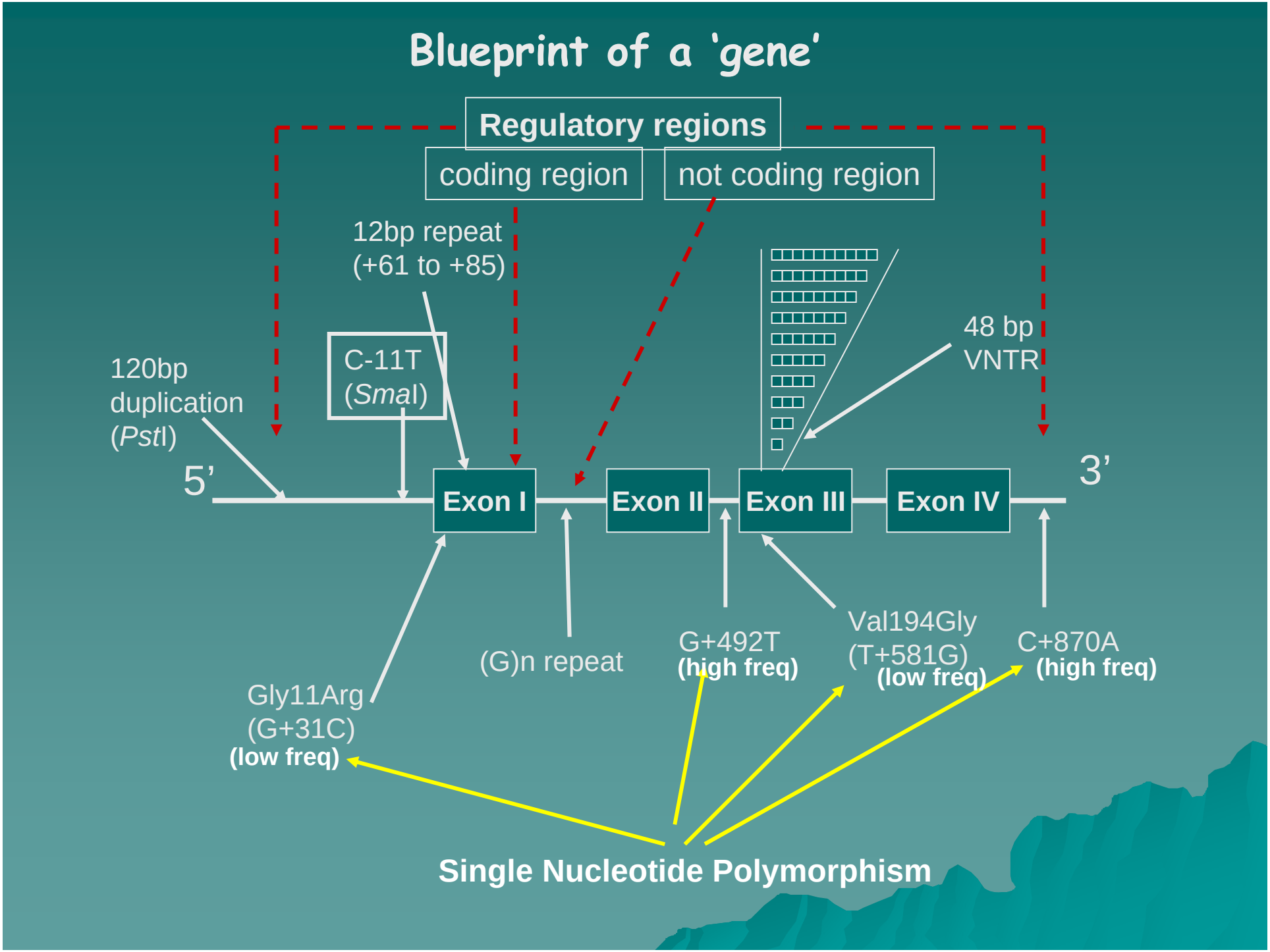

EM ITERATION 5
Red Blood Cell Hemoglobin Concentration
Red Blood Cell Volume
4.4
4.3
4.2
4.1
4
3.9
3.8
3.7
3.3
3.4
3.5
3.6
3.7
3.8
3.9
4


ANEMIA DATA WITH LABELS
Red Blood Cell Hemoglobin Concentration
Red Blood Cell Volume
4.4
4.3
4.2
4.1
4
3.9
3.8
3.7
3.3
3.4
3.5
3.6
3.7
3.8
3.9
4
Control Group
Anemia Group

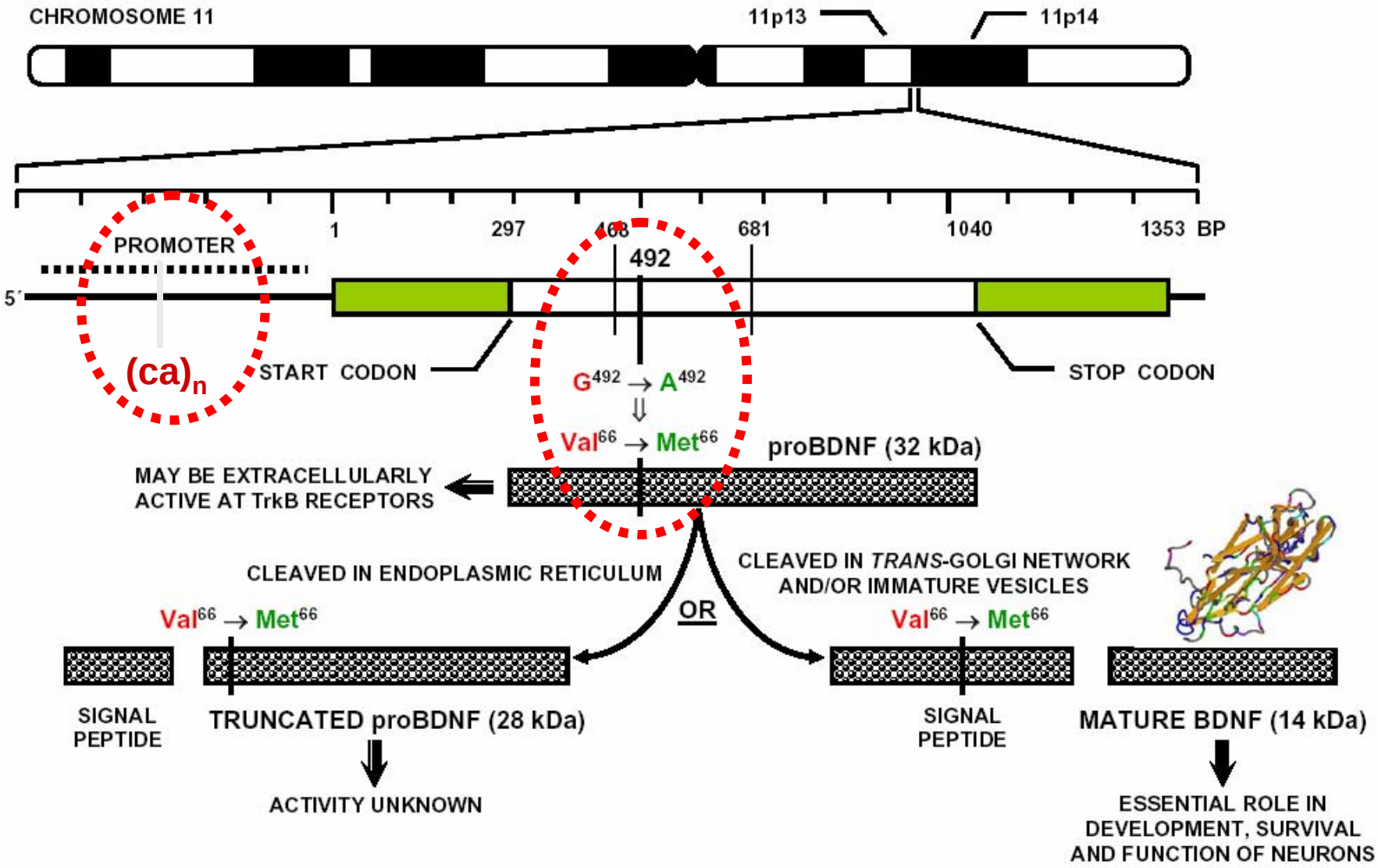
2D Transfer Function



- Segmentation

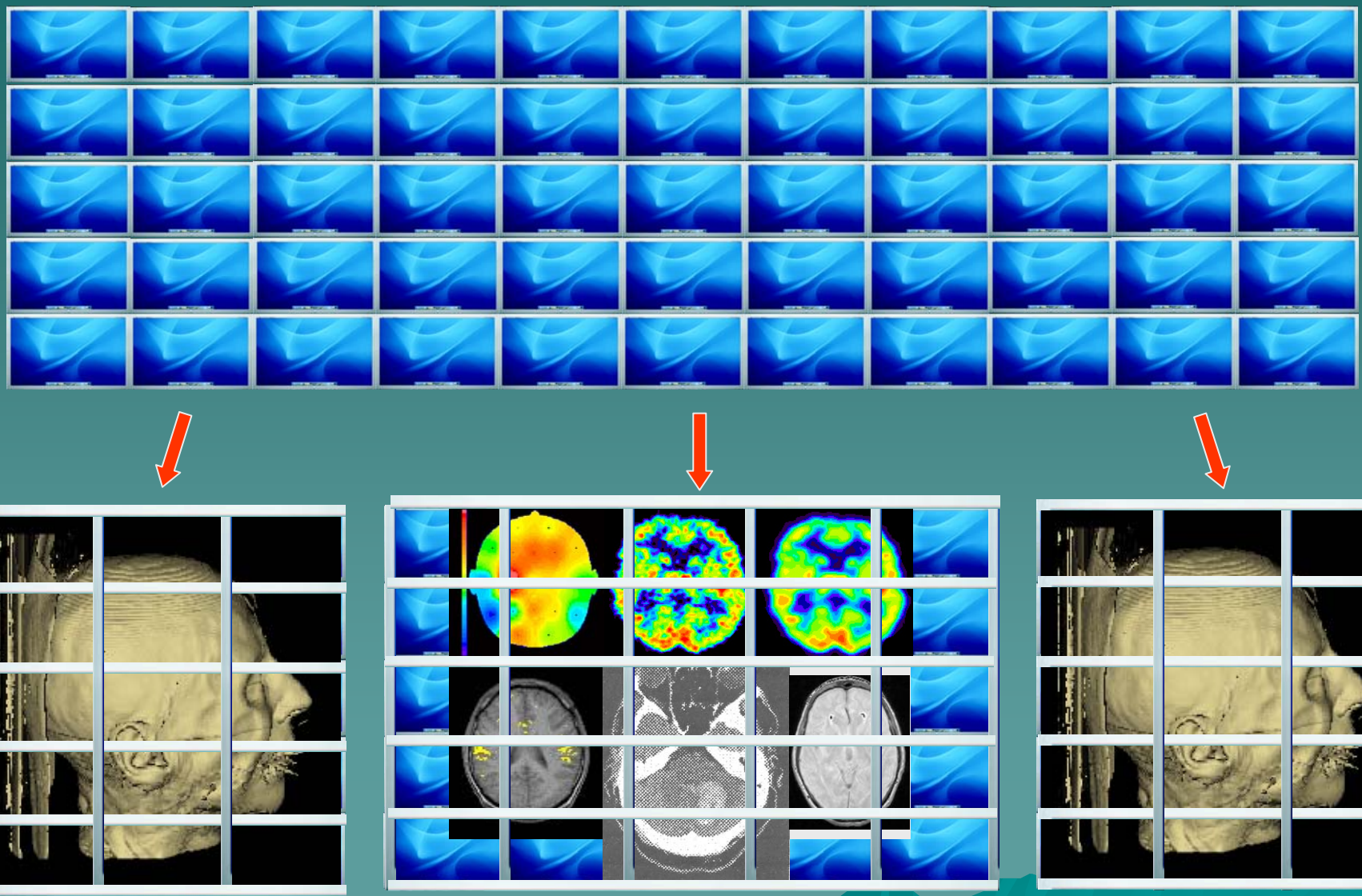

Blueprint of a 'gene'
Regulatory regions
coding region
not coding region
12bp repeat
(+61 to +85)
C-11T
(SmaI)
120bp
duplication
(PstI)
48 bp
VNTR
5'
3'
Exon I
Exon II
Exon III
Exon IV
Gly11Arg
(G+31C)
(low freq)
(G)n repeat
G+492T
(high freq)
Val194Gly
(T+581G)
(low freq)
C+870A
(high freq)
Single Nucleotide Polymorphism

The BDNF Gene



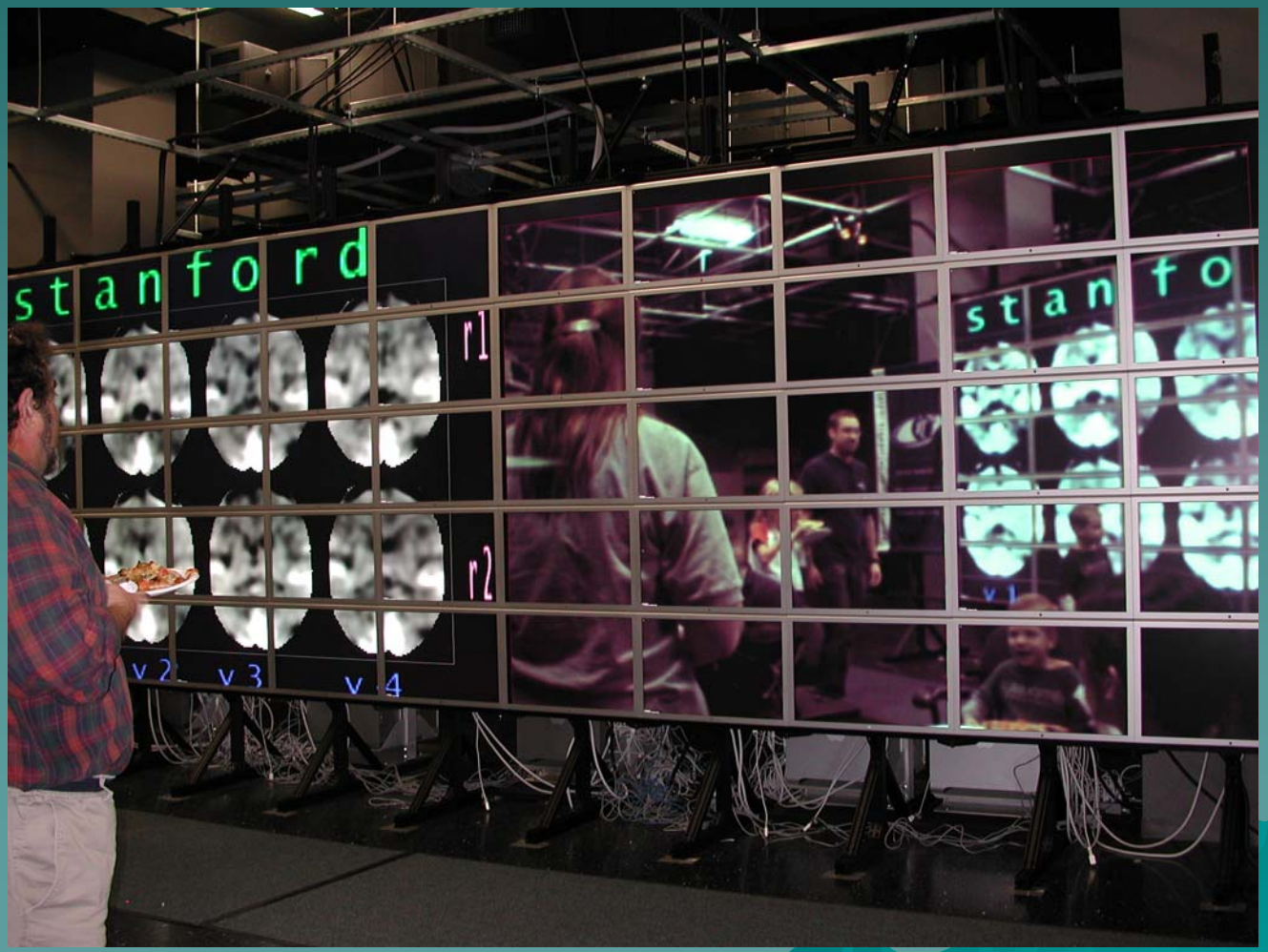
SOURCES: NCBI, ACCESSION # X60201; SHINTANI, ET AL. 1992; MURER, ET AL. 2001; MOWLA, ET AL. 2001

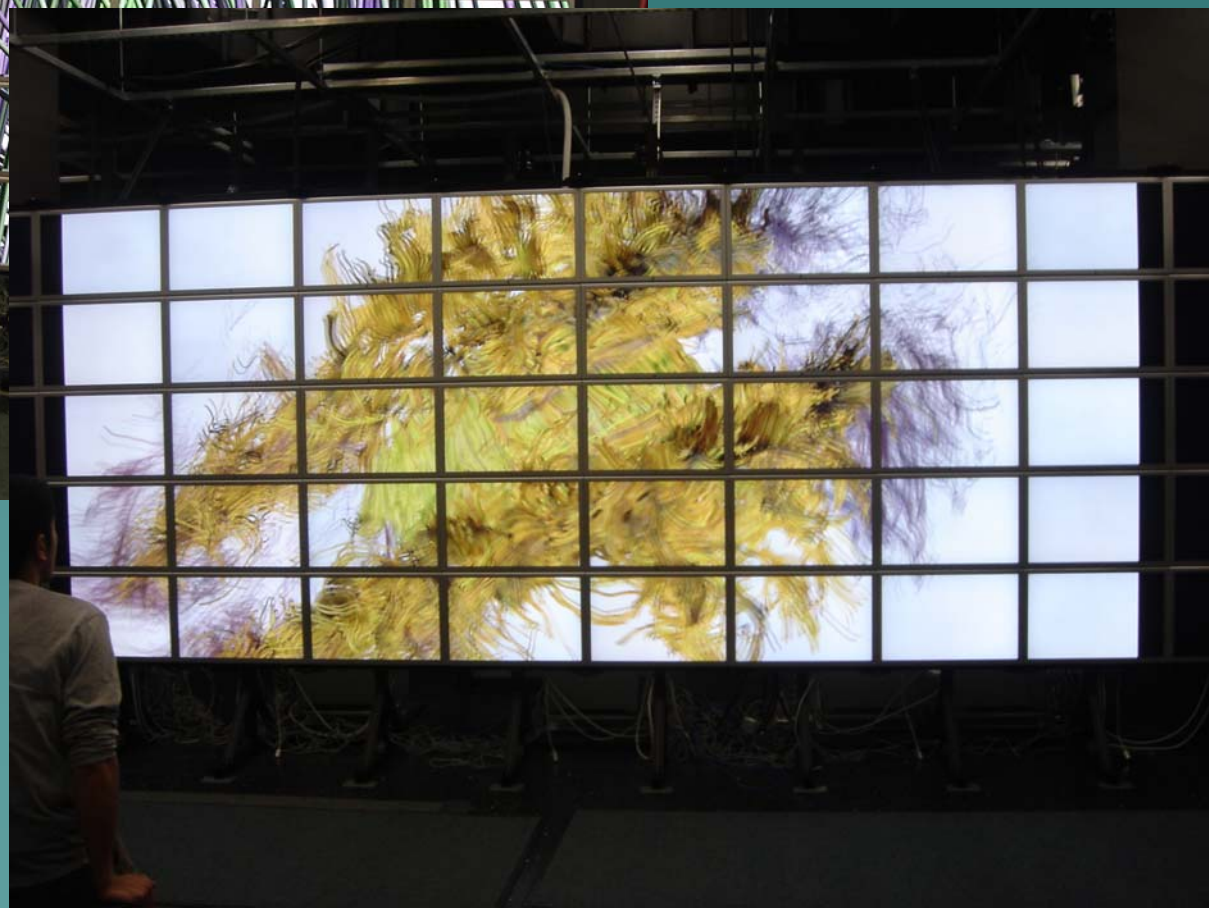
TIGC & HIPerWall

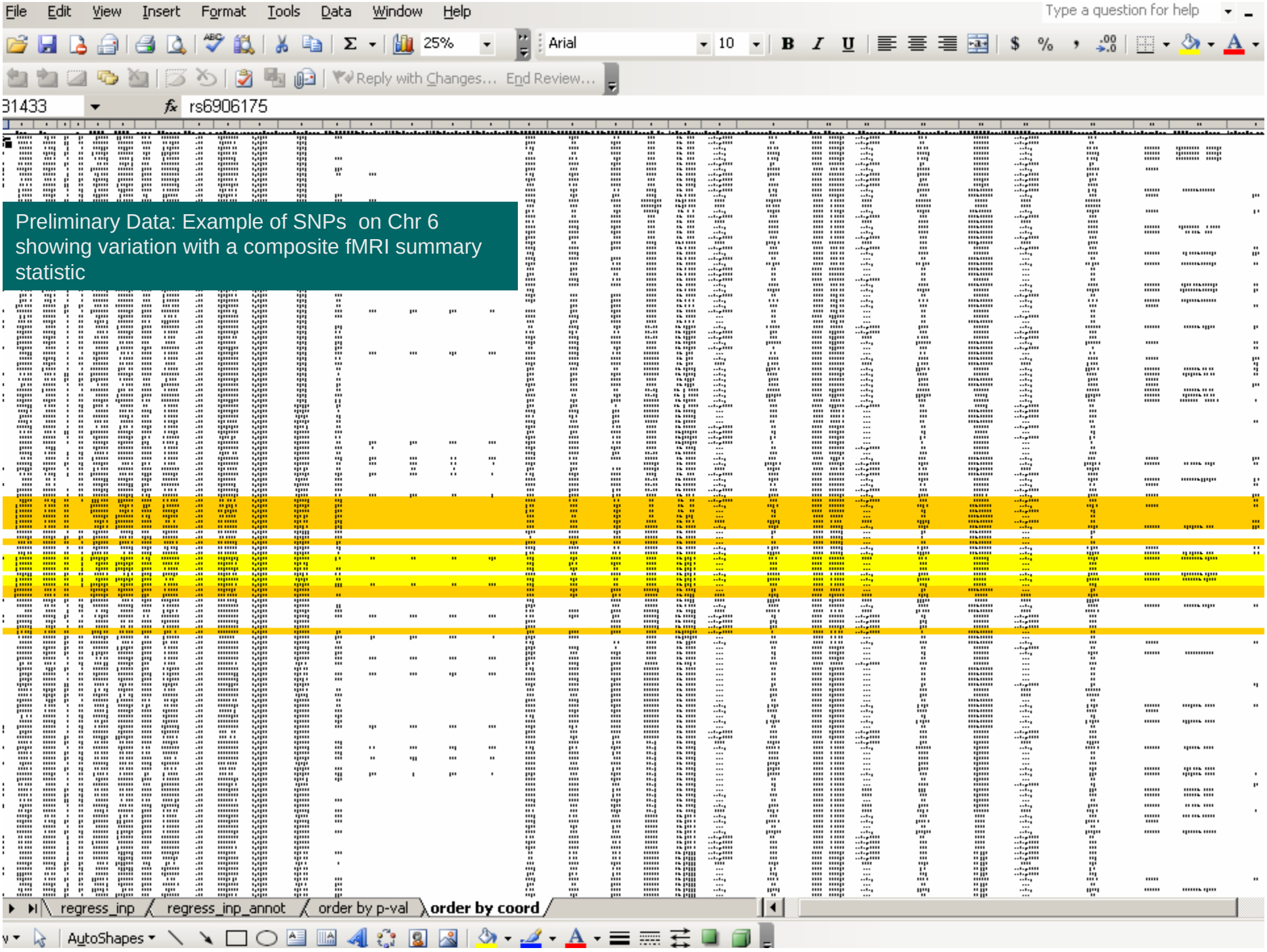


Developments

- Visualization: HiPerWall

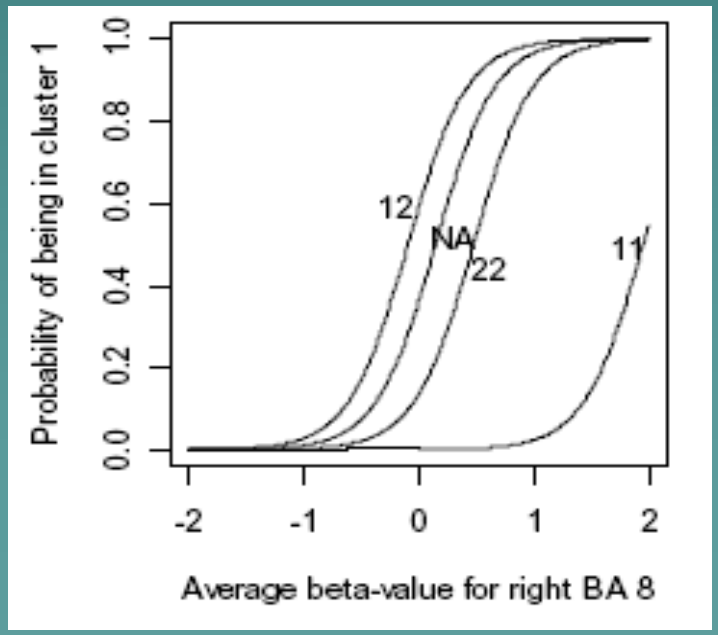


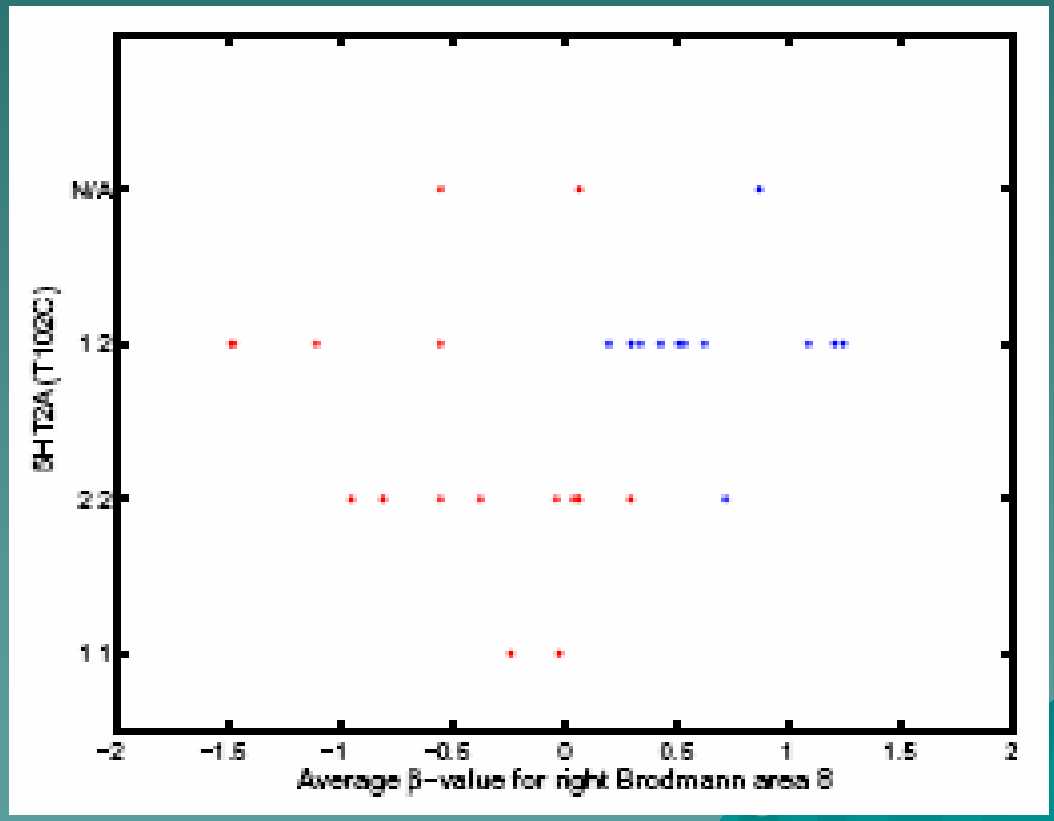



File Edit View Insert Format Tools Data Window Help
Type a question for help
25%
Arial
10
Reply with Changes... End Review...
31433
rs6906175
Preliminary Data: Example of SNPs on Chr 6 showing variation with a composite fMRI summary statistic
regress_inp
regress_inp_annot
order by p-val
order by coord
AutoShapes

Exploratory Data Analysis: Mixture models

Top: Clustering of 28 schizophrenics into 2 groups based on a single SNP and single ROI activation
Bottom: Probability of being in cluster 1 (blue) based on genotype and activation





Preliminary Results: Text Mining

- Extracted 60,000 abstracts from PubMed that contain the keyword “fMRI”
  - We fit a 200-topic statistical model using Bayesian methods
  - provides a full probabilistic model linking topics, words, documents, authors,….
  - A general basis for organizing/exploring text data sets, also for probabilistic query answering
  - Natural extension to include links to gene information

- Examples of automatically discovered topics: high probability words
  - Image Acquisition: echo weighted spin sequences images gradient sequence
  - Language Modeling: language left processing speech semantic activation words retrieval tasks
  - Cortical Regions: frontal temporal lobe left cortex parietal gyrus occipital regions anterior superior
  - fMRI Signal: fmri functional activation stimulation response bold signal cortex level dependent activity
  - Image Analysis: images method data registration algorithm reconstruction space error acquired phantom
  - Cognitive Function: cognitive memory impairment neuropsychological performance function deficits verbal
  - Clinical Care: cost diagnostic care screening health medical physicians quality management costs radiology
  - Image Models: models shape surface properties data parameters dimensional results distribution deformation derived geometry
  - Diagnosis: diagnosis differential diagnostic clinical considered correct confirmed suspected diagnoses history final suspicion cases signs definitive criteria laboratory
  - Surgery: surgical resection removal excision postoperative removed operative cases recurrence operation morbidity

Trans-disciplinary Example Publications

- Kim, S. Smyth, P., Stern, H., Turner, J., (2005) Parametric response surface models for analysis of multi-site fMRI data. *Proceedings of the 8th International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI).* Lecture Notes in Computer Science, Springer-Verlag, Berlin Heidelberg New York, 3749, 352-359.

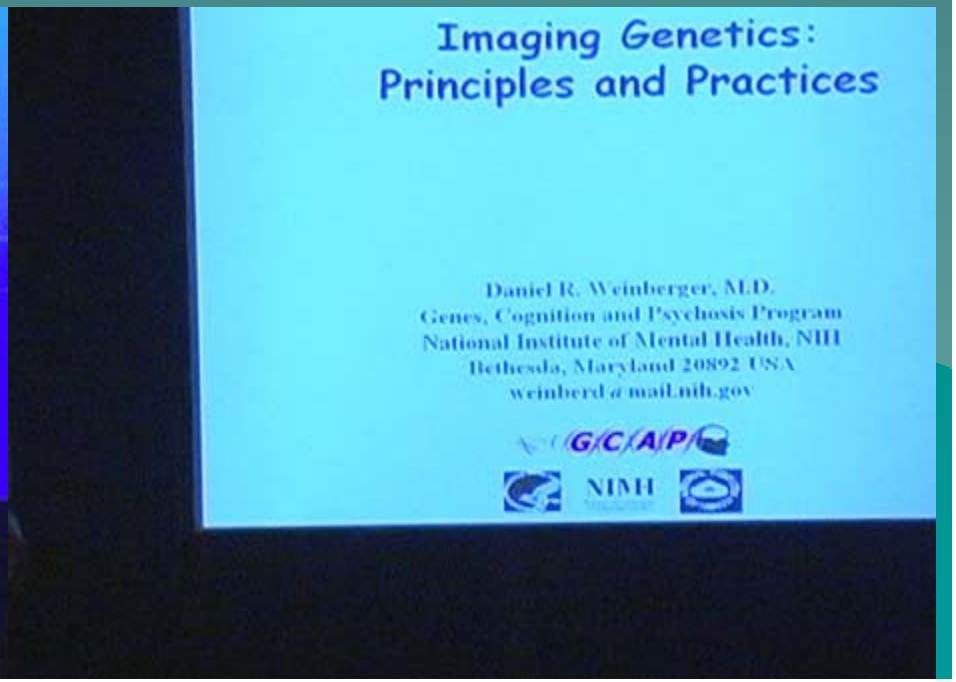
- Turner, J., Smyth, P., Fallon, J.F., Kennedy, J.L., Potkin, S.G., FIRST BIRN (2006). Imaging and genetics in schizophrenia. *Neuroinformatics, in press.*

Roadmap development

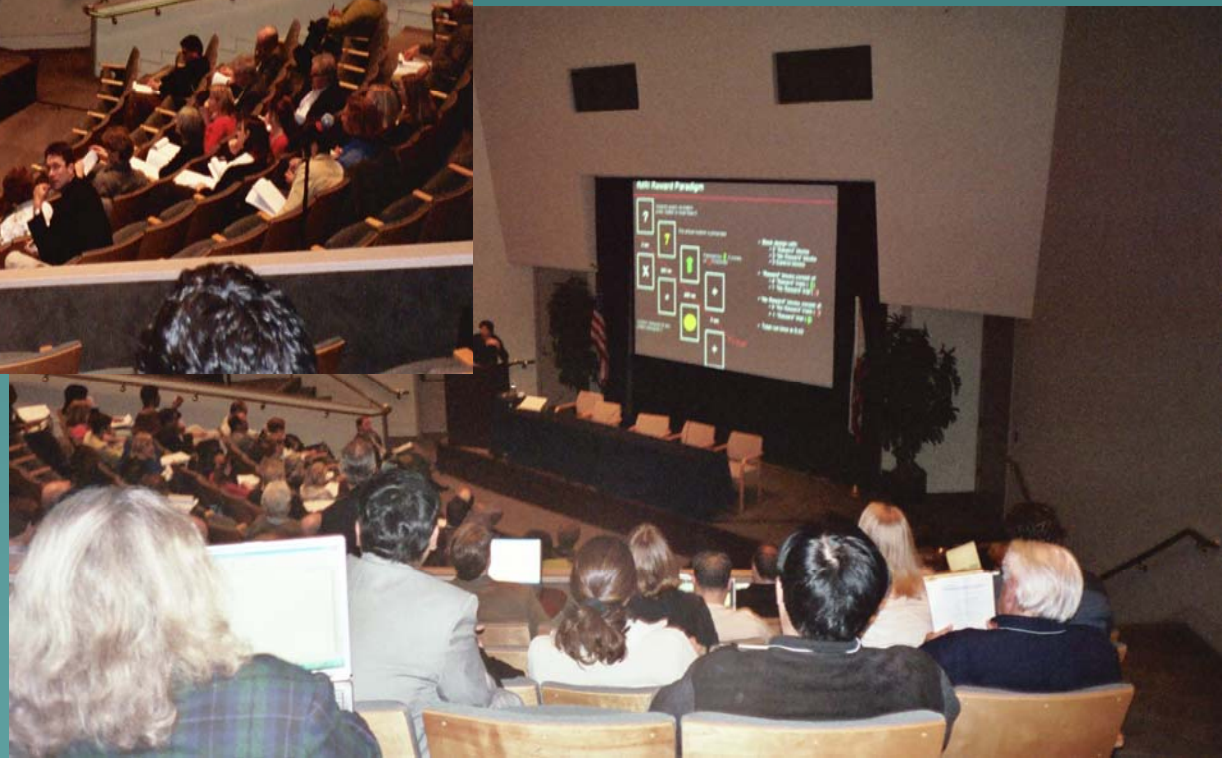
- External Advisory Board: Geneticists, imagers, clinicians, informatics experts
- EAB meeting: January 2005
- Roadmap implementation: summer 2005
- EAB teleconference: September 2005
- EAB meeting: January 2006
- Feedback leads to refinement of methods and approaches

Imaging Genetics Conference

- The **First** International Imaging Genetics Conference: January 17 and 18, 2005.
- The **Second** International Imaging Genetics conference: January 16 and 17, 2006.
- www.imaginggenetics.uci.edu

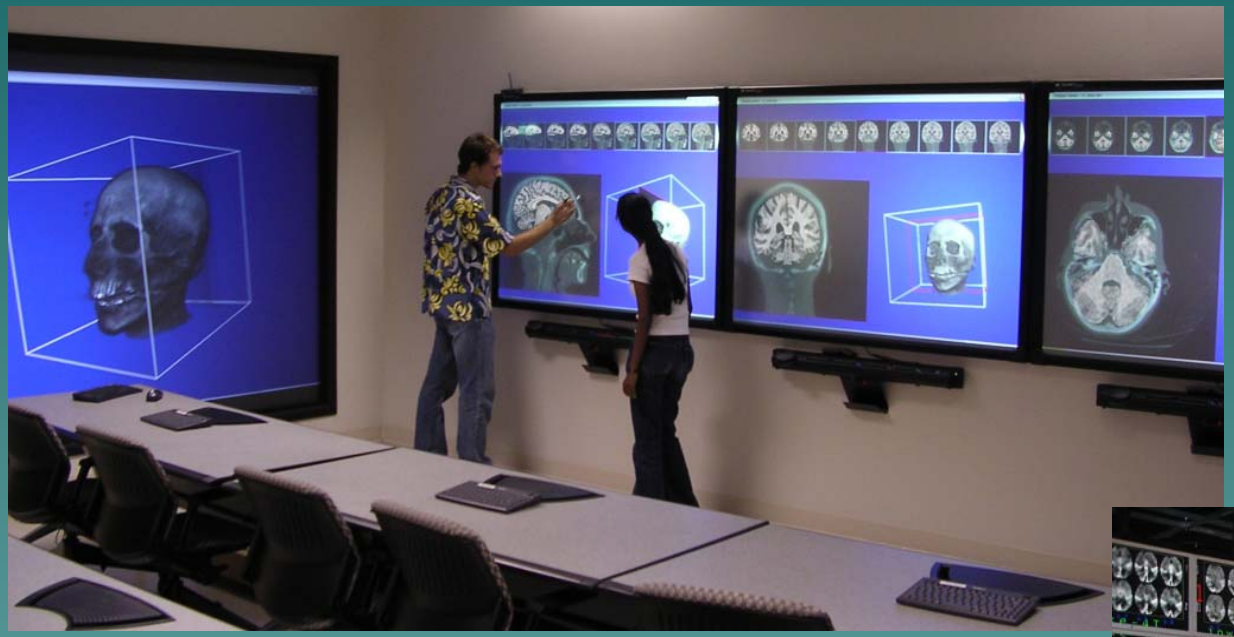


First and Second International Imaging Genetics Conferences



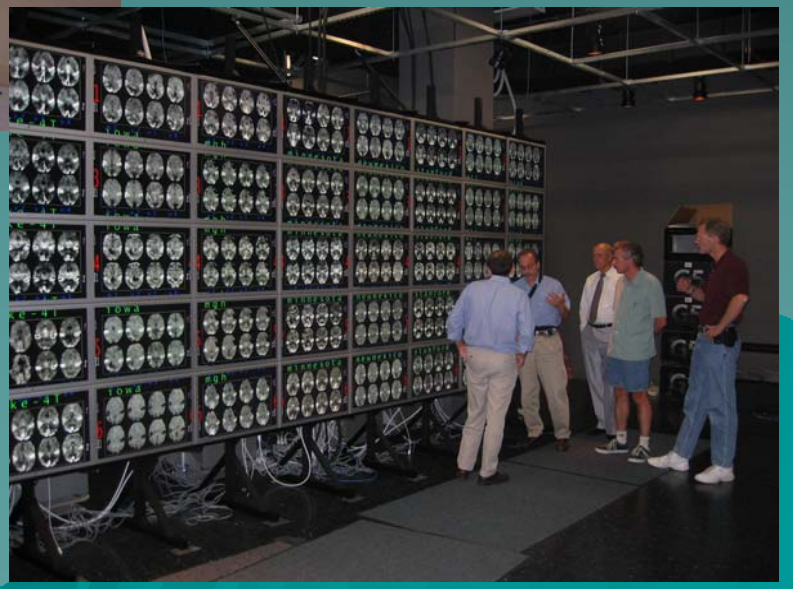
Preliminary Results: Visual Analytics

VizClass



OptIPuter

HIPerWall



- Collaboration between on-campus facilities
- Using OptIPuter to Enhance Collaboration

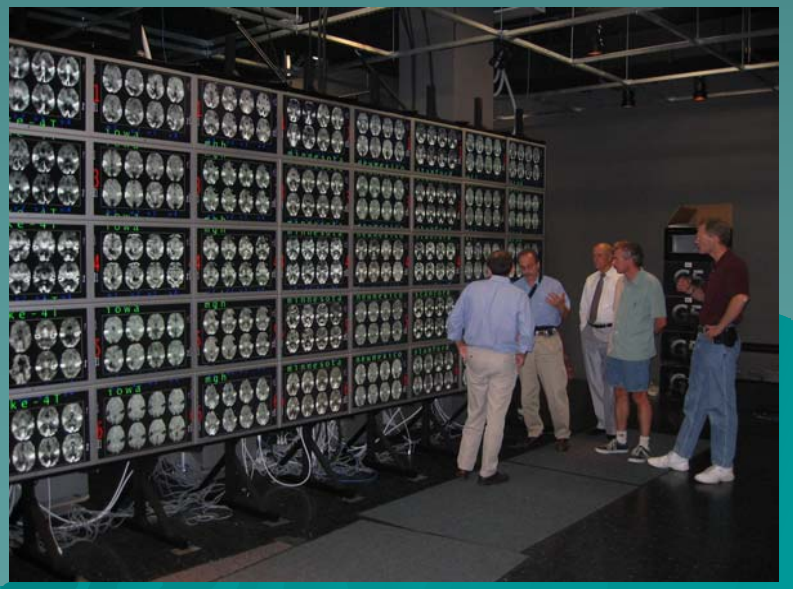
- Enable HCI Research

Metrics- Walk the Talk?

"Today the Calit2 institute at UCI was visited by two of Governor Arnold's advisors...We did a set of demos in Falko's lab …

As I was starting my "spiel", with the …image data behind me (and we also showed the 28 Sz images), the Chancellor walked in to the room (unexpectedly) and sat through the imaging part of the discussion …

There followed about 15 minutes of very interactive discussion between the 2 folks from Sacramento, the Chancellor, and myself and Falko – …

I think Falko and I "winged it" pretty well but it was handy to have the Chancellor there to chime in with comments from a medical perspective every now and again …

I certainly never imagined that I would end up explaining the 5 x 10 "mosaic" of image data to folks at this level!"